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(54) Titre : MODULATEURS DE CANAL IONIQUE
(54) Title: ION CHANNEL MODULATORS

(57) Abrégé/Abstract:
The invention relates to compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The compounds, compositions, and methods described herein can be used for the therapeutic modulation of ion channel function, and treatment of disease and disease symptoms, particularly those mediated by certain calcium channel subtype targets.

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(54) Title: ION CHANNEL MODULATORS

(57) Abstract: The invention relates to compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The compounds, compositions, and methods described herein can be used for the therapeutic modulation of ion channel function, and treatment of disease and disease symptoms, particularly those mediated by certain calcium channel subtype targets.

ION CHANNEL MODULATORS

BACKGROUND

All cells rely on the regulated movement of inorganic ions across cell membranes to perform essential physiological functions. Electrical excitability, synaptic plasticity, and signal transduction are examples of processes in which changes in ion concentration play a critical role. In general, the ion channels that permit these changes are proteinaceious pores consisting of one or multiple subunits, each containing two or more membrane-spanning domains. Most ion channels have selectivity for specific ions, primarily Na^+, K^+, Ca^{2+}, or Cl^-, by virtue of physical preferences for size and charge. Electrochemical forces, rather than active transport, drive ions across membranes, thus a single channel may allow the passage of millions of ions per second. Channel opening, or "gating" is tightly controlled by changes in voltage or by ligand binding, depending on the subclass of channel. Ion channels are attractive therapeutic targets due to their involvement in so many physiological processes, yet the generation of drugs with specificity for particular channels in particular tissue types remains a major challenge.

Voltage-gated ion channels open in response to changes in membrane potential. For example, depolarization of excitable cells such as neurons result in a transient influx of Na^+ ions, which propagates nerve impulses. This change in Na^+ concentration is sensed by voltage-gated K^+ channels, which then allow an efflux of K^+ ions. The efflux of K^+ ions repolarizes the membrane. Other cell types rely on voltage-gated Ca^{2+} channels to generate action potentials. Voltage-gated ion channels also perform important functions in non-excitable cells, such as the regulation of secretory, homeostatic, and mitogenic processes. Ligand-gated ion channels can be opened by extracellular stimuli such as neurotransmitters (e.g., glutamate, serotonin, acetylcholine), or intracellular stimuli (e.g. cAMP, Ca^{2+}, and phosphorylation).

The Ca_v1 family of voltage-gated calcium channels consists of 4 main subtypes $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$ and $Ca_v1.4$. These currents are primarily found in skeletal muscle for $Ca_v1.1$, heart, smooth muscle, brain, pituitary and adrenal tissue for $Ca_v1.2$, brain pancreas, heart, kidney, ovary and cochlea for $Ca_v1.3$ and in retina for

$Ca_v1.4$. These currents require a strong depolarization for activation and are long lasting. The subunit composition of the Ca_v1 channels is defined by their α_1 subunit, which forms the pore and contains the voltage-sensing gates ($\alpha_1 1.1$, $\alpha_1 1.2$, $\alpha_1 1.3$ and $\alpha_1 1.4$, also known as α_{1S}, α_{1C}, α_{1D}, and α_{1F} respectively) and the β, $\alpha_2\delta$ and γ subunits.

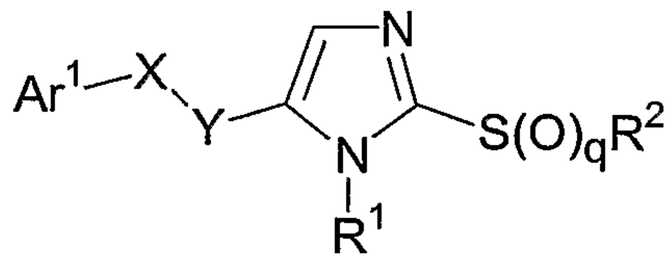
Genetic or pharmacological perturbations in ion channel function can have dramatic clinical consequences. Long QT syndrome, epilepsy, cystic fibrosis, and episodic ataxia are a few examples of heritable diseases resulting from mutations in ion channel subunits. Toxic side affects such as arrhythmia and seizure which are triggered by certain drugs are due to interference with ion channel function (Sirois, J.E. and, Atchison, W.D., *Neurotoxicology* 1996; 17(1):63-84; Keating, M.T., *Science* 1996 272:681-685). Drugs are useful for the therapeutic modulation of ion channel activity, and have applications in treatment of many pathological conditions, including hypertension, angina pectoris, myocardial ischemia, asthma, bladder overactivity, alopecia, pain, heart failure, dysmenorrhea, type II diabetes, arrhythmia, graft rejection, seizure, convulsions, epilepsy, stroke, gastric hypermotility, psychoses, cancer, muscular dystrophy, and narcolepsy (Coghlan, M.J., et al. *J. Med. Chem.* 2001, 44:1627-1653; Ackerman. M.J., and Clapham, D.E. *N. Eng. J. Med.* 1997, 336:1575-1586). The growing number of identified ion channels and understanding of their complexity will assist in future efforts at therapies, which modify ion channel function.

Overactive bladder (OAB) is characterized by storage symptoms such as urgency, frequency and nocturia, with or without urge incontinence, resulting from the overactivity of the detrusor muscle in the bladder. OAB can lead to urge incontinence. The etiology of OAB and painful bladder syndrome is unknown, although disturbances in nerves, smooth muscle and urothelium can cause OAB (Steers, W. *Rev Urol*, 4:S7-S18). There is evidence to suggest that reduction of bladder hyperactivity may be indirectly effected by inhibition of $Ca_v2.2$ and/or Ca_v1 channels.

SUMMARY

The invention relates to heterocyclic compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The compounds and compositions comprising them are useful for treating disease or disease symptoms, including those mediated by or associated with ion channels.

In one aspect is a compound of formula (AI) or pharmaceutical salt thereof



(AI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3, $C(R^3)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0, 1 or 2;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar^1 is aryl or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3; and

Y is C=O;

Wherein, R^1 is aryl or heteroaryl, each optionally substituted with one or more substituents;

Wherein, each R^2 is independently $(CH_2)_mAr^3$; and
each Ar^3 is heteroaryl optionally substituted with one or more substituents;

Wherein, Ar^3 is a heteroaryl comprising a five-membered ring having carbon atoms and 1, 2 or 3 heteroatoms selected from N, O and S, optionally substituted with one or more substituents;

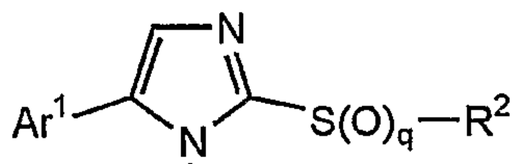
Wherein, Ar^3 is pyrrolidinyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, or benzthiazolyl, each optionally substituted with one or more substituents;

Wherein each R^2 is $(CH_2)_nNR^3R^4$, wherein each R^4 is independently $(CH_2)_pAr^3$;

Wherein R^3 is H;

Wherein the compound of formula AI is a compound delineated in any of the tables herein, or pharmaceutical salt thereof.

In one aspect is a compound of formula (BI) or pharmaceutical salt thereof



(BI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl,

alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

q is 0, 1 or 2;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, with the proviso that Ar^3 is not piperidinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl;

each Z is independently selected from O or NR^3;

each m is 1 or 2;

each n is 2 or 3;

each p is 0 or 1;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen,

OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

q is 0;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, with the proviso that Ar^3 is not piperidinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl;

each Z is independently selected from O or NR^3;

each m is 1 or 2;

each n is 2 or 3;

each p is 0 or 1;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy;

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

q is 1;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, with the proviso that when R^2 is $(CH_2)_mAr^3$ and m is 1, then Ar^3 is not ortho dimethylaminophenyl;

each Z is independently selected from O or NR^3;

each m is 1 or 2;

each n is 2 or 3;

each p is 0 or 1;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy;

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

q is 2;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each Z is independently selected from O or NR^3;

each m is 1 or 2;

each n is 2 or 3;

each p is 0 or 1;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected

from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy;

Wherein,

R^2 is $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, or $(CH_2)_mCONR^3R^4$, and m is 2;

Wherein,

R^1 is Ar^2 or lower alkyl substituted with Ar^2, R^2 is $(CH_2)_mAr^3$, and m is 1, with the proviso that R^1 is not furylmethyl or tetrahydrofurylmethyl;

Wherein,

R^1 is Ar^2 or lower alkyl substituted with Ar^2,

R^2 is $(CH_2)_mAr^3$, and m is 2, with the proviso that R^1 is not furylmethyl or tetrahydrofurylmethyl;

Wherein,

Ar^1 and R^1 are each an optionally substituted aryl, and R^2 is independently selected from $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

Wherein,

each R^2 is independently selected from $(CH_2)_mAr^3$, and each Ar^3 is heteroaryl optionally substituted with one or more substituents;

Wherein,

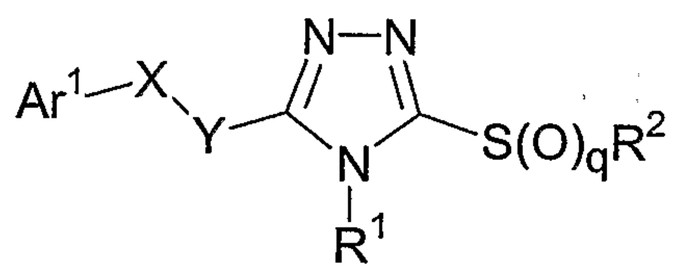
Ar^3 is heteroaryl having a five-membered ring of carbon atoms and 1, 2 or 3 heteroatoms selected from N, O and S, optionally substituted with one or more substituents;

Wherein,

Ar^3 is pyrrolidinyl, pyrazolyl, imidazolyl, thioimidazolyl, benzimidazolyl, or benzthioimidazolyl, each optionally substituted with one or more substituents;

Wherein, the compound of formula BI is a compound delineated in any of the tables herein or pharmaceutical salt thereof.

One aspect is a method of treating a disease or disease symptom in a subject including administering to the subject an effective amount a compound of formula CI or pharmaceutical salt thereof:



(CI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3, $C(R^3)_2$, S, a bond or O, or together with Y forms -CH=CH-;

Y is C=O, a bond, or lower alkyl, or together with X forms -CH=CH-;

R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0,1 or 2;

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$, $(CH_2)_nOR^4$; $(CH_2)_mCN$; alkyl; alkynyl, $(CR^3R^3)_mCONR^3R^4$, Ar^4, $(CR^3R^3)_mN(R^3)C(O)Ar^3$, or $(CH_2)_mC(NOH)NH_2$;

each R^3 is independently H, or lower alkyl;

each R^4 is independently H, lower alkyl, alkoxy, $(CH_2)_n NR^5R^6$, or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently C_3-C_6 cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

In other aspects, the methods are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar^1 is aryl or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3;

Y is lower alkyl;

R^1 is aryl optionally substituted with one or more substituents; and

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, or $(CH_2)_nNR^3R^4$.

Wherein,

Ar^1 is aryl or heteroaryl, each optionally substituted with one or more substituents;

X is a bond;

Y is a bond;

R^1 is aryl optionally substituted with one or more substituents; and

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$;

Wherein, each R^2 is independently selected from $(CH_2)_mAr^3$;

Wherein,

each R^2 is independently selected from $(CH_2)_mAr^3$; and

each Ar^3 is heteroaryl optionally substituted with one or more substituents;

Wherein Ar^3 is a heteroaryl comprising a five-membered ring having carbon atoms and 1, 2 or 3 heteroatoms selected from N, O and S, optionally substituted with one or more substituents;

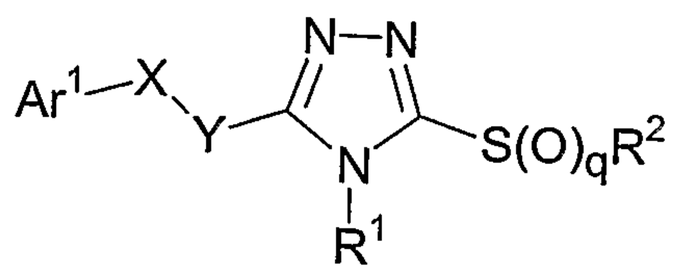
Wherein Ar^3 is pyrrolidinyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, or benzthiazolyl, each optionally substituted with one or more substituents;

Wherein the compound of formula CI is a compound delineated in any of Tables C1, or pharmaceutical salt thereof;

Another aspect is a method of modulating calcium channel activity comprising contacting a calcium channel with a compound of any of the formulae herein.

Another aspect is a compound of formula CI above, or pharmaceutical salt thereof.

Another aspect is a compound of formula CI or pharmaceutical salt thereof,



(CI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is CH_2;

Y is a bond;

R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0,1 or 2;

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, or $(CH_2)_mCONR^3R^4$;

each R^3 is independently H, or lower alkyl;

each R^4 is independently H, lower alkyl, alkoxy, $(CH_2)_n NR^5R^6$, or $(CH_2)_pAr^3$;

m is 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-

methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently C_3-C_6 cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is a bond;

Y is a bond;

R^1 is Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is 4-pyridylmethyl;

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom, however, Ar^1 is not 4-pyridyl;

X is a bond;

Y is a bond;

R^1 is Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents; and

each R^2 is 3-pyridylmethyl;

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is a bond;

Y is a bond;

R^1 is Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents; and

each R^2 is 2-pyridylmethyl;

Wherein:

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

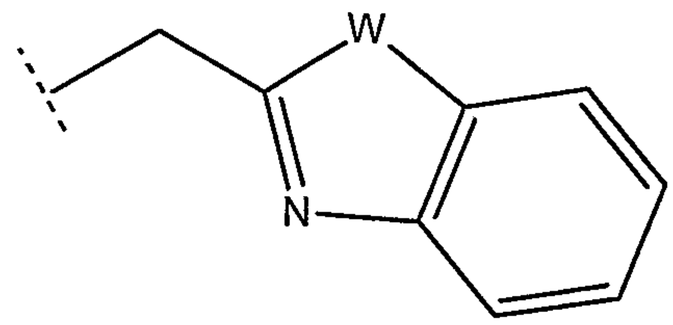
X is a bond;

Y is a bond;

R^1 is Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents; and

each R^2 is:



wherein W is NR^3, S or O.

Wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is a bond;

Y is a bond;

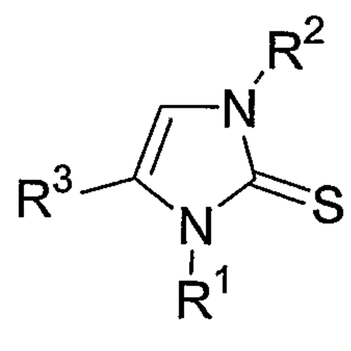
R^1 is Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is $(CH_2)_mAr^3$; and

each Ar^3 is aryl substituted with NH_2, $S(O)_2OR^3$, COOH, or $C(O)NH_2$;

One aspect is a compound of formula D- (I) or pharmaceutical salt thereof



D-(I)

wherein,

R^3 is Ar^1 or Ar^1-X-Y wherein,

each Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^4, $C(R^4)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is independently selected from $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$, $(CH_2)_mC(O)NR^4R^5$, $(CH_2)_nNR^4R^5$, $(CH_2)_3Ar^3$, or $(CH_2)_mAr^3$;

each R^4 is independently selected from H, or lower alkyl;

each R^5 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^6$, NR^6R^7, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^6$, $C(O)NR^6R^7$, $OC(O)NR^6R^7$, $NR^6C(O)NR^6R^7$, $C(NR^6)NR^6R^7$, $NR^6C(NR^7)NR^6R^7$, $S(O)_2NR^6R^7$, R^8, $C(O)R^8$, $NR^6C(O)R^8$, $S(O)R^8$, or $S(O)_2R^8$;

each R^6 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^8 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently

selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

q is 0 or 1.

Another aspect is a compound of any of the formulae herein (including any combinations thereof),

wherein R^3 is Ar^1 and R^1 is Ar^2;

wherein

R^3 is independently, aryl or heteroaryl, each optionally substituted with one or more substituents; and

R^1 is independently, aryl or heteroaryl, each optionally substituted with one or more substituents;

wherein R^2 is $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$ or $(CH_2)_mC(O)NR^4R^5$;

wherein R^2 is $(CH_2)_mAr^3$ and Ar^3 is aryl or heteroaryl each optionally substituted with one or more substituents;

wherein R^2 is $(CH_2)_mC(O)NR^4R^5$ and R^5 is independently $(CH_2)_pAr^3$, wherein Ar^3 is aryl or heteroaryl, each optionally substituted with one or more substituents;

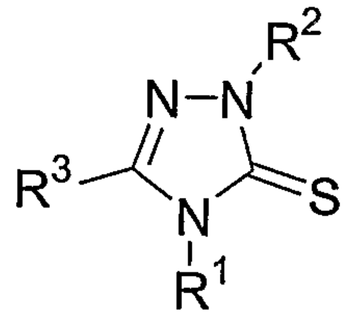
wherein R^2 is $(CH_2)_nNR^4R^5$ or $(CH_2)_mAr^3$;

wherein m is 2 and Ar^3 is a heteroaryl comprising a five-membered ring having carbon atoms and 1, 2 or 3 heteroatoms selected from N, O and S, optionally substituted with one or more substituents;

wherein Ar^3 is pyrrolidinyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, benzimidazolyl, benzoxazolyl, or benzthiazolyl, each optionally substituted with one or more substituents; or

wherein the compound of formula D-I is a compound of any of Tables D- (1-6).

One aspect is a compound of formula E-(I) or pharmaceutical salt thereof



E-(I)

wherein,

R^3 is alkyl, alkoxyalkyl, Ar^1 or Ar^1-X-Y wherein,

each Ar^1 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^4, $C(R^4)_2$, or O;

Y is C=O or lower alkyl;

R^1 is H, alkenyl, Ar^2 or lower alkyl optionally substituted with Ar^2

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is independently selected from H, $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$, $(CH_2)_mC(O)NR^4R^5$, $(CH_2)_mC(O)N(OR^4)R^5$, $(CH_2)_mCH_2OR^4$, Ar^3, $(CH_2)_nAr^3$; $(CH_2)_nNR^4R^5$, or $(CH_2)_mAr^3$;

each R^4 is independently selected from H, or lower alkyl;

each R^5 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^6$, NR^6R^7, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^6$, $C(O)NR^6R^7$, $OC(O)NR^6R^7$, $NR^6C(O)NR^6R^7$, $C(NR^6)NR^6R^7$, $NR^6C(NR^7)NR^6R^7$, $S(O)_2NR^6R^7$, R^8, $C(O)R^8$, $NR^6C(O)R^8$, $S(O)R^8$, or $S(O)_2R^8$;

each R^6 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^8 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

q is 0 or 1.

Another aspect is a compound of any of the formulae herein (including any combinations thereof):

wherein, R^3 is Ar^1 and R^1 is Ar^2;

wherein,

R^3 is independently, aryl or heteroaryl, each optionally substituted with one or more substituents; and

R^1 is independently, aryl or heteroaryl, each optionally substituted with one or more substituents;

wherein R^2 is $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$ or $(CH_2)_mC(O)NR^4R^5$;

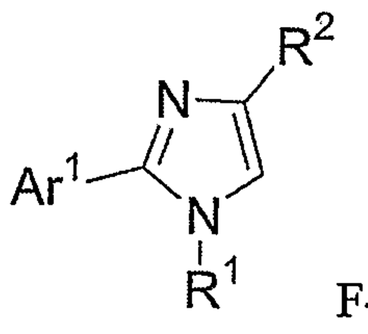
wherein R^2 is $(CH_2)_mAr^3$ and Ar^3 is aryl or heteroaryl each optionally substituted with one or more substituents;

wherein R^2 is $(CH_2)_mC(O)NR^4R^5$ and R^5 is independently $(CH_2)_pAr^3$, wherein Ar^3 is aryl or heteroaryl, each optionally substituted with one or more substituents;

wherein R^2 is $(CH_2)_nNR^4R^5$ or $(CH_2)_mAr^3$; or

wherein the compound of formula E-I is any of those in the tables herein.

In one aspect is a method for treating a disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound of formula F-(I) or pharmaceutical salt thereof:



F-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl,

alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, Ar^3, $CH_2NR^3R^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

In other aspects, the methods are those having any of the formulae herein (including any combinations thereof):

Wherein,

each R^2 is independently $CONR^3R^4$, Ar^3, $CH_2NR^3R^4$;

Wherein,

Ar^1 is aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 ; and

Ar^2 is independently aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

Wherein,

each R^2 is independently Ar^3; and

each Ar^3 is independently aryl or heteroaryl, each optionally substituted with one or more substituents;

Wherein,

each Ar^3 is independently heteroaryl, each optionally substituted with one or more substituents;

Wherein,

each R^2 is independently $CONR^3R^4$; and

each R^4 is $(CH_2)_pAr^3$;

Wherein,

each Ar^3 is independently aryl or heteroaryl, each optionally substituted with one or more substituents;

Wherein,

Ar^3 is independently a nitrogen-containing heteroaryl, optionally substituted with one or more substituents;

Wherein,

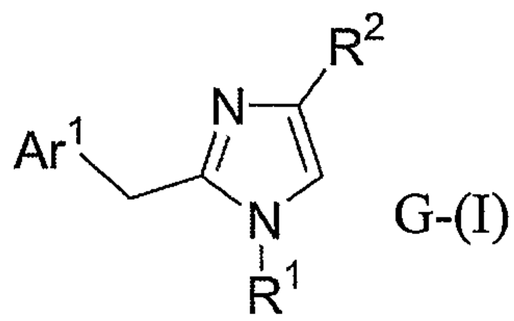
each R^2 is independently $CH_2NR^3R^4$; and

each R^4 is $(CH_2)_pAr^3$;

Wherein,

Ar^3 is independently a nitrogen-containing heteroaryl, optionally substituted with one or more substituents.

In one aspect is a compound of formula G-(I) or pharmaceutical salt thereof



G-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_nNR^3R^4$ or CH_2OR^4;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each n is independently 1 or 2;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

Wherein

Ar^1 is aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2;

Ar^2 is independently selected from aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl; and

each R^2 is independently selected from $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, or $(CH_2)_nNR^3R^4$;

Wherein,

Ar^1 is aryl, which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

Ar^2 is independently aryl, which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl,

cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl; and

each R^2 is independently selected from $(CH_2)_mAr^3$, or $(CH_2)_nNR^3R^4$;

Wherein,

each Ar^3 is independently aryl or heteroaryl, each optionally substituted with one or more substituents;

Wherein,

each R^4 is $(CH_2)_pAr^3$; and

each Ar^3 is independently aryl or heteroaryl, each optionally substituted with one or more substituents;

Wherein,

each R^2 is independently selected $(CH_2)_nNR^3R^4$; and

each R^4 is $(CH_2)_pAr^3$;

Wherein,

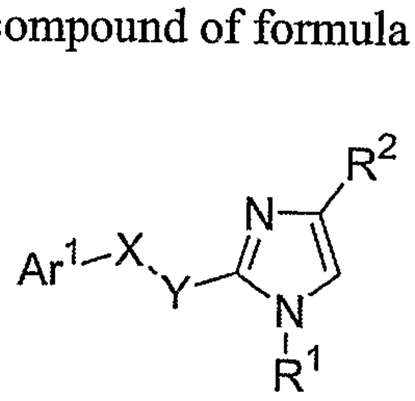
R^1 is para-chlorophenyl;

Wherein,

Ar^1 is para-fluorophenyl;

Wherein, the compound of formula G-I is a compound delineated in any of the tables herein, or pharmaceutical salt thereof.

In one aspect is a compound of formula H-(I) or pharmaceutical salt thereof



H-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

X is NR^3, $C(R^3)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $CH_2NR^3R^4$ or CH_2OR^4;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

Wherein,

Ar^1 is aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

X is NR^3;

Y is C=O or lower alkyl;

R^1 is Ar^2;

Ar^2 is independently aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl; and

each R^2 is independently $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, or $CH_2NR^3R^4$;

Y is C=O; and

Ar^2 is independently aryl which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

Wherein,

Y is lower alkyl;

R^1 is Ar^2;

Ar^2 is independently aryl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

Wherein,

each R^2 is independently $CONR^3R^4$ or $CH_2NR^3R^4$;

Wherein,

each R^2 is independently $(CH_2)_mAr^3$;

Wherein,

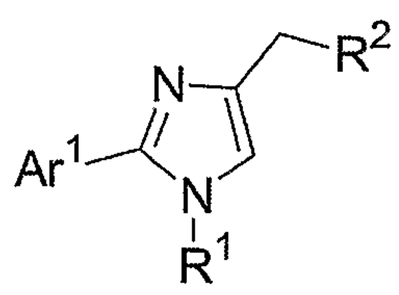
Ar^3 is heteroaryl optionally substituted with one or more substituents;

Wherein,

each R^4 is independently $(CH_2)_pAr^3$;

Wherein the compound of formula H-I is a compound delineated in any of the tables herein, or pharmaceutical salt thereof.

One aspect is a compound of formula J-(I) or pharmaceutical salt thereof



J- (I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl, or heteroaryl each optionally substituted with one or more substituents;

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$; $(CH_2)_nOR^3$; $(CH_2)_nAr^3$ or $(CH_2)_nNR^3R^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2)R^7$ or $(CH_2)_pAr^3$; or

each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atom in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or more lower alkyl groups;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each n is independently 1 or 2;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

Other aspects are those compounds (of any of the formulae herein (including any combinations thereof):

Wherein each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_nAr^3$ or $(CH_2)_nNR^3R^4$;

Wherein,

R^1 is C_1-C_2 alkyl substituted with Ar^2; and

Ar^2 is optionally substituted with one or more substituents;

Wherein,

R^1 is Ar^2;

Ar^2 is optionally substituted with one or more substituents;

Wherein,

R^2 is $(CH_2)_mC(O)OR^3$, $(CH_2)_mC(O)Ar^3$ or $(CH_2)_mC(O)NR^3R^4$ and each m is independently 0 or 1; and

each Ar^3 is optionally substituted with one or more substituents;

wherein,

R^2 is $(CH_2)_nNR^3R^4$ and n is 1;

Wherein,

R^2 is $(CH_2)_nNR^3R^4$ and n is 2;

Wherein,

R^2 is $(CH_2)_mAr^3$ and m is 0; and

Ar^3 is optionally substituted with one or more substituents;

Wherein,

R^2 is $(CH_2)_mAr^3$ and m is 1; and

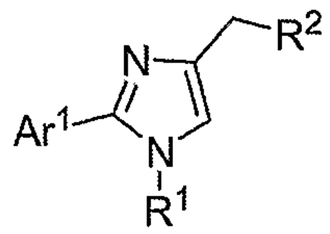
Ar^3 is optionally substituted with one or more substituents;

Wherein,

each Ar^1, Ar^2, Ar^3 and Ar^4 is independently selected from cycloalkyl, phenyl, naphthyl, acenaphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo-[b]furanyl, benzo[b]thiophenyl, 1H-

indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, tetrahydro-iso quinolinyl, isoquinolinyl, tetrahydro-quinoline, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, or phenoxazinyl , each optionally substituted with one or more substituents;

Wherein, the compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is aryl or heteroaryl each optionally substituted with one to three substituents;

R^1 is Ar^2;

each Ar^2 is independently selected from aryl or heteroaryl each optionally substituted with one to three substituents;

R^2 is $(CH_2)_nNR^3R^4$ and n is 1 wherein,

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2)R^7$ or $(CH_2)_pAr^3$; or

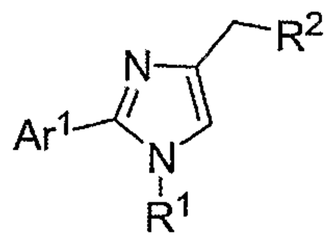
each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atom in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or two lower alkyl groups;

each p is independently 0 or 1; and

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents;

Wherein the compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is aryl or heteroaryl each optionally substituted with one to three substituents;

R^1 is Ar^2;

each Ar^2 is independently selected from aryl or heteroaryl each optionally substituted with one to three substituents;

R^2 is $(CH_2)_nNR^3R^4$ and n is 2 wherein,

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2)R^7$ or $(CH_2)_pAr^3$; or

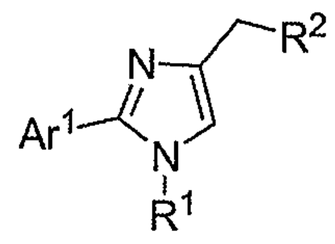
each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atoms in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or two lower alkyl groups;

each p is independently 0 or 1; and

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents;

Wherein the compound is of formula J- (I) :



J- (I)

wherein,

Ar^1 is aryl or heteroaryl each optionally substituted with one to three substituents;

R^1 is Ar^2;

each Ar^2 is independently selected from heterocyclyl or heteroaryl each optionally substituted with one to three substituents;

R^2 is $(CH_2)_mAr^3$ and m is 0;

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, OR^5, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

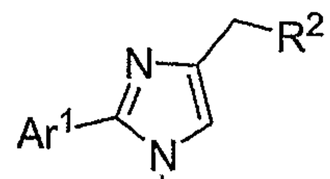
each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each p is independently 0 or 1; and

each Ar^4 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents independently selected halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

Wherein the compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is aryl or heteroaryl each optionally substituted with one to three substituents;

R^1 is Ar^2;

each Ar^2 is independently selected from heterocyclyl or heteroaryl each optionally substituted with one to three substituents;

R^2 is $(CH_2)_mAr^3$ and m is 1;

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, OR^5, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

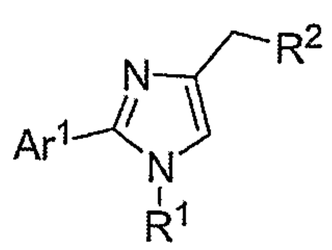
each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each p is independently 0 or 1; and

each Ar^4 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents independently selected halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

Wherein the compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is phenyl substituted with one to three substituents;

R^1 is Ar^2 and Ar^2 phenyl substituted with one to three substituents;

R^2 is $(CH_2)_nNR^3R^4$ and n is 1;

each R^3 is independently selected from H or lower alkyl;

each R^4 is $(CH_2)_pAr^3$;

each p is independently 0 or 1;

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents;

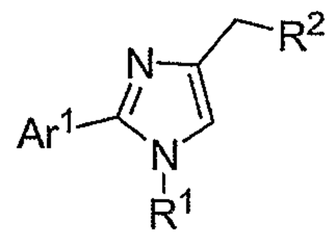
each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, OR^5, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino; and

each Ar^4 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents independently selected halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

Wherein the compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is phenyl substituted with one to three substituents;

R^1 is Ar^2 and Ar^2 phenyl substituted with one to three substituents;

R^2 is $(CH_2)_nNR^3R^4$ and n is 1;

each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atoms in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or two lower alkyl groups;

each substituent for Ar^1 and Ar^2 is independently selected from halogen, OR^5, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy

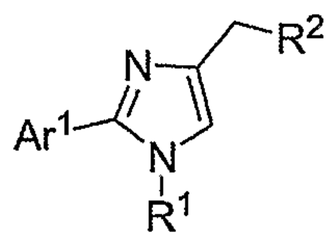
each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each p is independently 0 or 1; and

each Ar^4 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents independently selected halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

Wherein compound is of formula J- (I):



J- (I)

wherein,

Ar^1 is phenyl substituted with one to three substituents;

R^1 is Ar^2 and Ar^2 phenyl substituted with one to three substituents;

R^2 is $(CH_2)_mAr^3$ and m is 0;

each Ar^3 is benzimidazol-2-yl optionally substituted with one to three substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is each independently selected from halogen, OR^5, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents selected form halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino;

each p is independently 0 or 1; and

each Ar^4 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents independently selected halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy; or

Wherein the compound of formula J- (I) is any of those in Table J-1 herein.

Another aspect is a method of treating a Cav1 calcium channel mediated disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound, or pharmaceutical salt, (or composition thereof) of any of the formulae herein.

Another aspect is a method of modulating (e.g., inhibiting, agonism, antagonism) calcium channel activity including contacting a compound, or pharmaceutical salt thereof, of any of the formulae herein (or composition thereof) with a calcium channel.

In the methods herein, the calcium channel can be Ca_v1 (e.g., $Ca_v1.2$ or $Ca_v1.3$). The Ca_v1 calcium channel mediated disease or disease symptom can be a nervous system disease or disease symptom or can be a cardiovascular disease or disease symptom.

Another aspect is a method of treating a mediated disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound, or pharmaceutical salt, (or composition thereof) of any of the formulae

herein. The disease or disease symptom is angina, hypertension, congestive heart failure, myocardial ischemia, atrial fibrillation, diabetes mellitus, urinary incontinence, overactive bladder, pulmonary disease, cognitive function, or a nervous system disorder;

Wherein, the disease or disease symptom is modulated by calcium channel Cav1; Wherein the disease or disease symptom is modulated by calcium channel Cav1.2 or Cav1.3; Wherein the disease or disease symptom is angina, hypertension, congestive heart failure, myocardial ischemia, arrhythmia, diabetes, urinary incontinence, stroke, pain, traumatic brain injury, or a neuronal disorder.

Another aspect is a composition including a compound of any of the formulae herein, or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The composition can further include an additional therapeutic agent.

Another aspect is a method of making a compound of any of the formulae herein, including reacting an intermediate delineated herein with a reagent to provide a compound of any of the formulae herein as defined herein.

Another aspect is a method of modulating (e.g., inhibiting, antagonism, agonism) calcium channel activity in a subject in need thereof comprising administering to the subject an effective amount of a compound of any of the formulae herein, or pharmaceutically acceptable salt thereof, or composition thereof.

In other aspects, the invention relates to a composition comprising a compound of any of the formulae herein, an additional therapeutic agent, and a pharmaceutically acceptable carrier. The additional therapeutic agent can be a cardiovascular disease agent and/or a nervous system disease agent. A nervous system disease agent refers to a peripheral nervous system (PNS) disease agent and/or a central nervous system (CNS) disease agent.

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having a disease or disease symptom (including, but not limited to angina, hypertension, congestive heart failure, myocardial ischemia, atrial fibrillation, diabetes mellitus, urinary incontinence, overactive bladder, pulmonary disease, cognitive function, or a nervous system disorder). The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care

professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having an ion channel mediated disease or disease symptom (including, but not limited to angina, hypertension, congestive heart failure, myocardial ischemia, atrial fibrillation, diabetes mellitus, urinary incontinence, overactive bladder, pulmonary disease, cognitive function, or a nervous system disorder). The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

The invention also relates to a method of making a compound described herein, the method including any reactions or reagents as delineated in the schemes or examples herein. Alternatively, the method includes taking any one of the intermediate compounds described herein and reacting it with one or chemical reagents in one or more steps to produce a compound described herein.

Also within the scope of this invention is a packaged product. The packaged product includes a container, one of the aforementioned compounds in the container, and a legend (e.g., a label or an insert) associated with the container and indicating administration of the compound for treating a disorder associated with ion channel modulation.

In other embodiments, the compounds, compositions, and methods delineated herein are any of the compounds of the Tables herein or methods including them.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

As used herein, the term "halo" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_5 indicates that the group may have from 1 to 5 (inclusive) carbon atoms in it. The term "lower alkyl" refers to a C_1-C_6 alkyl chain. The term "arylalkyl" refers to a moiety in which an alkyl hydrogen atom is replaced by an aryl group.

The term "alkoxy" refers to an -O-alkyl radical. The term "alkylene" refers to a divalent alkyl (i.e., -R-). The term "alkylenedioxo" refers to a divalent species of the structure -O-R-O-, in which R represents an alkylene.

The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbon.

The term "aryl" refers to a 6-membered monocyclic or 10- to 14-membered multicyclic aromatic hydrocarbon ring system wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl and the like.

The term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

The term "substituents" refers to a group "substituted" on an alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$. Each R^5 is independently hydrogen, C_1-C_4 alkyl or C_3-C_6 cycloalkyl. Each R^6 is independently hydrogen, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R^7 is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^5, R^6 and R^7 can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, or 1,2-methylenedioxy.

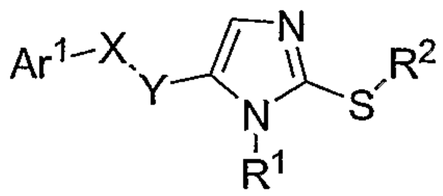
In one aspect, the substituents on a group are independently, hydrogen, hydroxyl, halogen, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, alkyl (C1-C6 straight or branched), alkoxy (C1-C6 straight or branched), O-benzyl, O-phenyl, phenyl, 1,2-methylenedioxy, carboxyl, morpholinyl, piperidinyl, amino or $OC(O)NR^5R^6$. Each R^5 and R^6 is as described above.

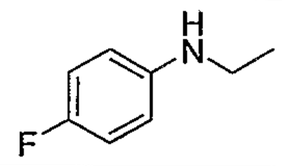
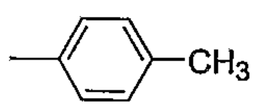
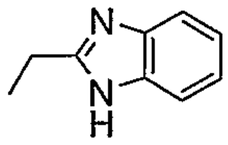
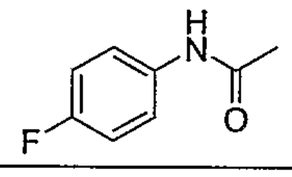
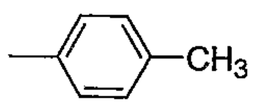
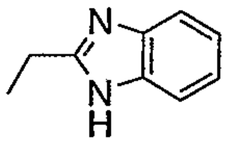
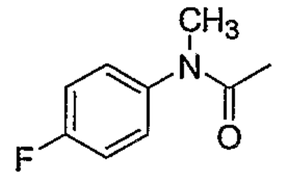
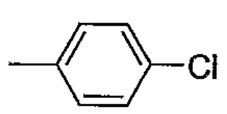
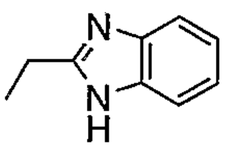
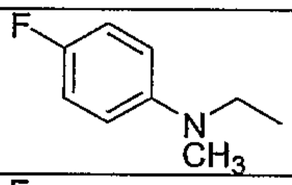
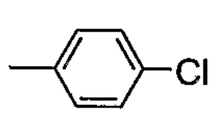
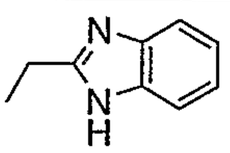
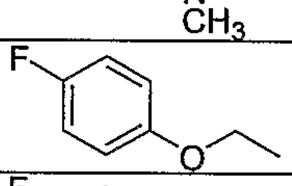
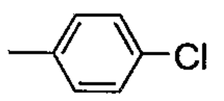
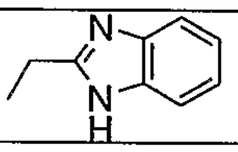
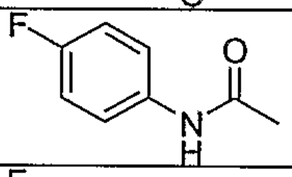
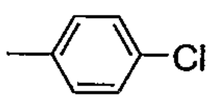
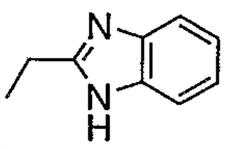
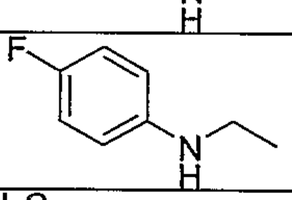
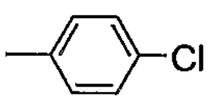
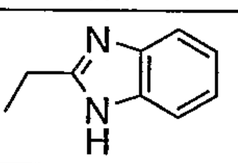
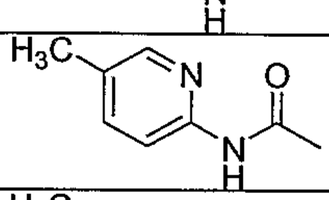
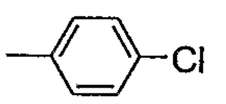
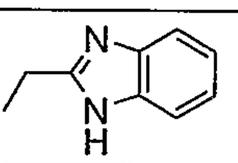
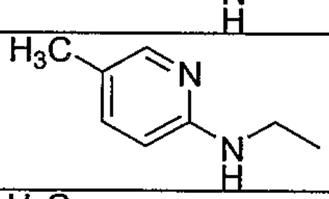
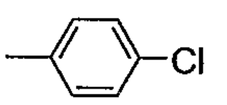
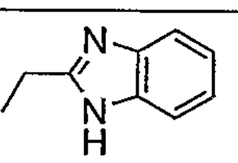
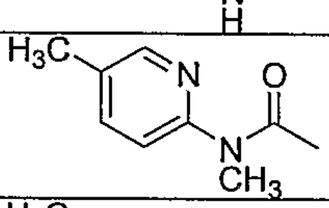
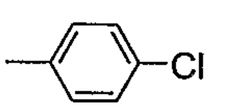
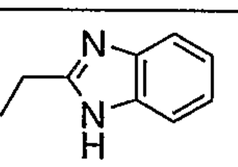
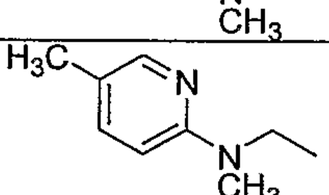
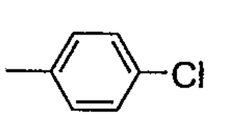
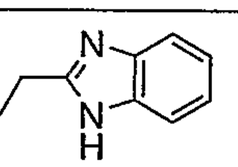
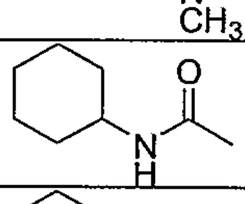
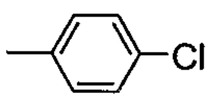
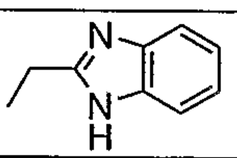
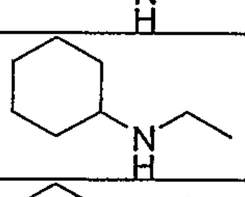
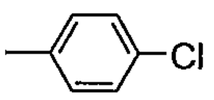
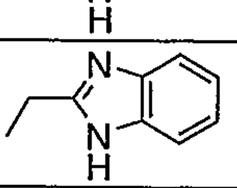
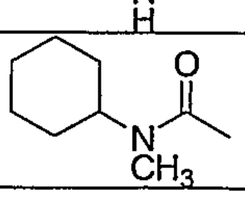
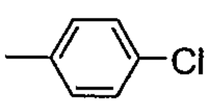
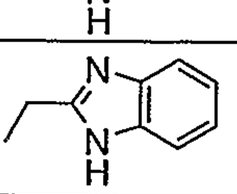
The term "treating" or "treated" refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease, the symptoms of the disease or the predisposition toward the disease.

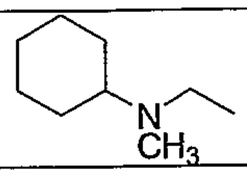
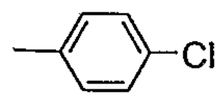
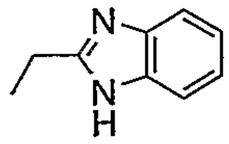
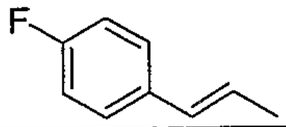
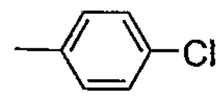
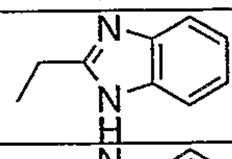
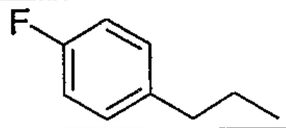
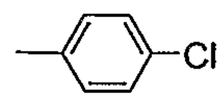
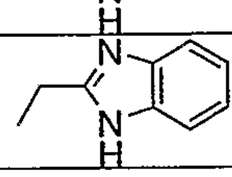
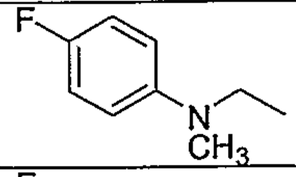
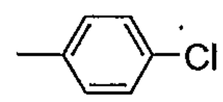
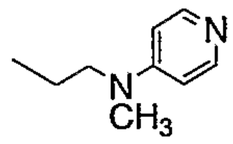
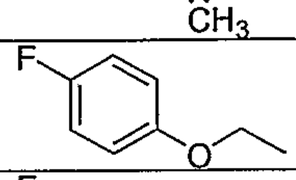
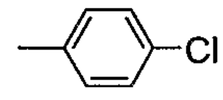
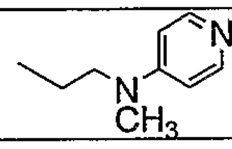
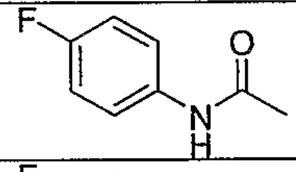
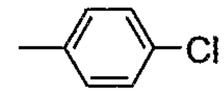
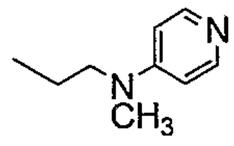
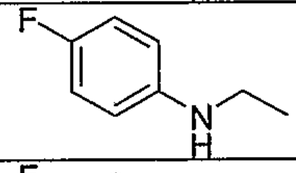
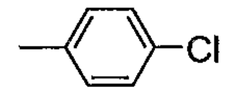
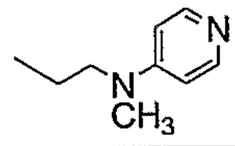
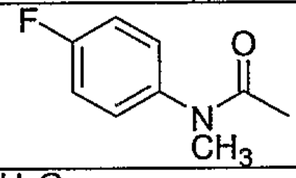
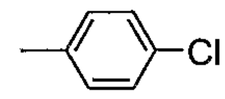
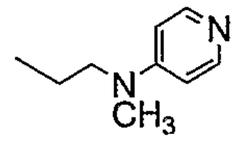
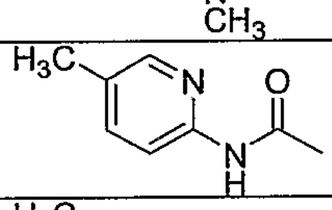
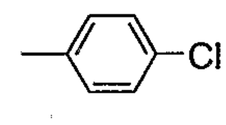
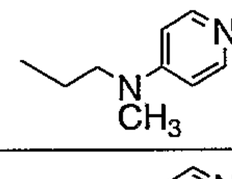
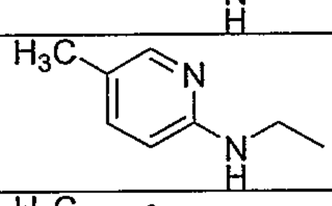
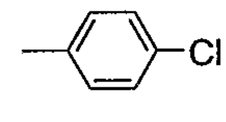
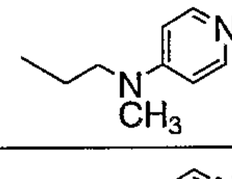
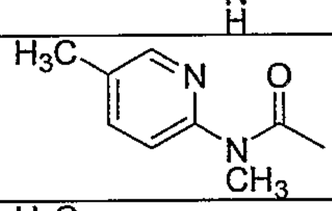
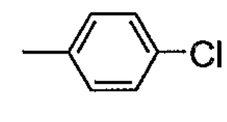
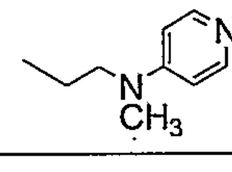
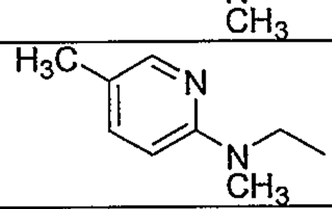
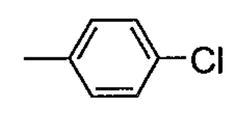
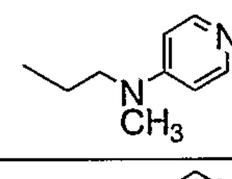
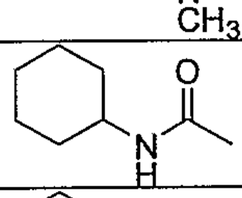
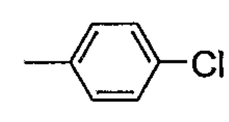
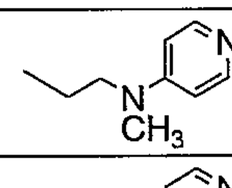
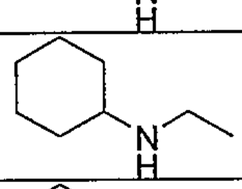
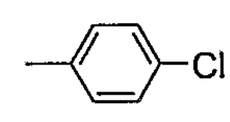
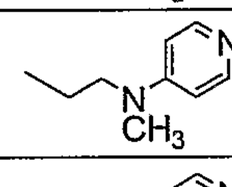
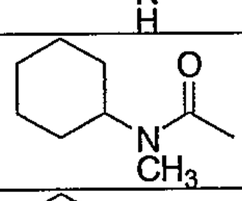
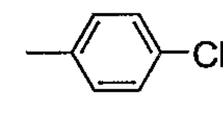
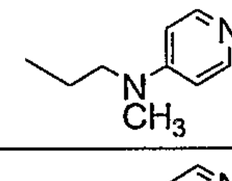
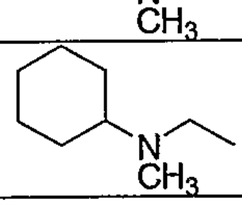
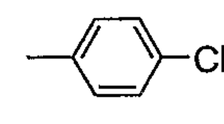
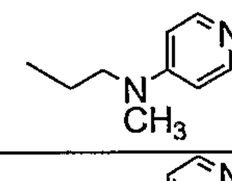
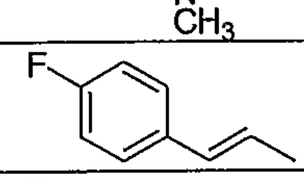
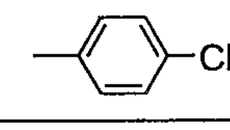
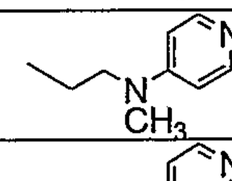
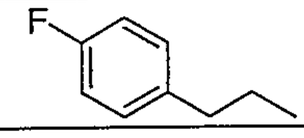
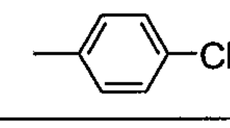
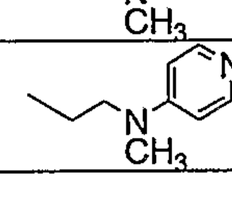
"An effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

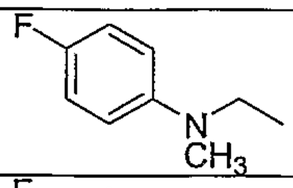
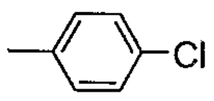
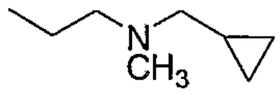
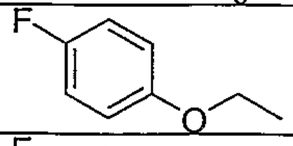
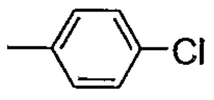
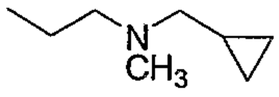
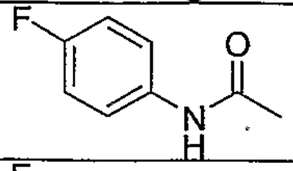
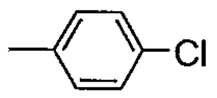
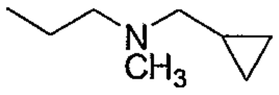
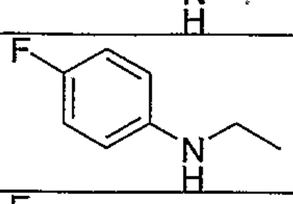
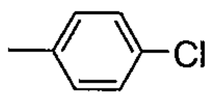
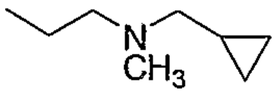
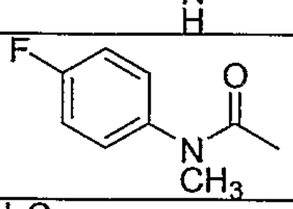
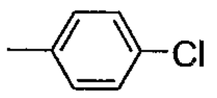
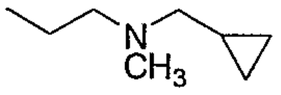
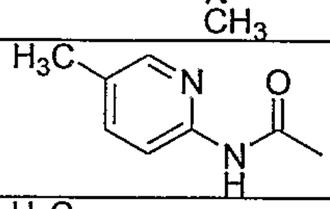
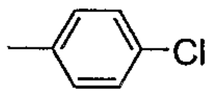
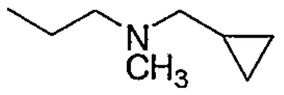
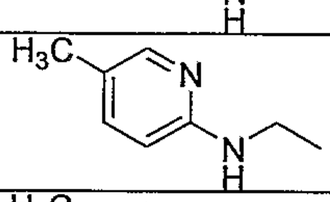
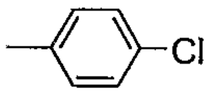
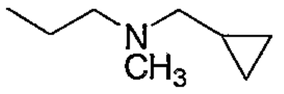
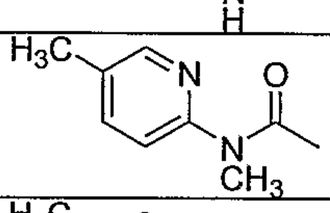
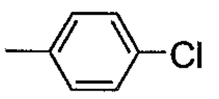
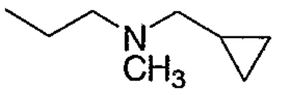
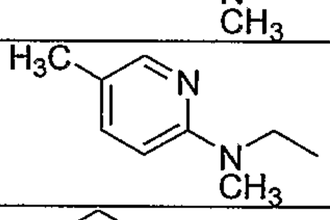
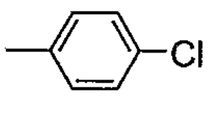
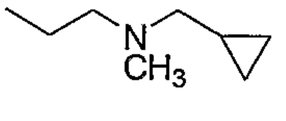
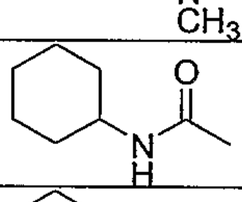
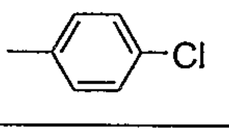
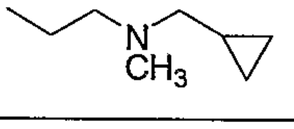
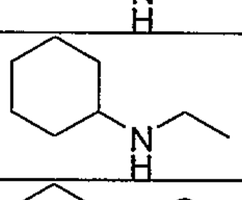
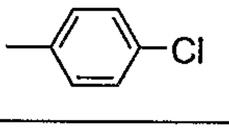
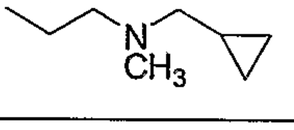
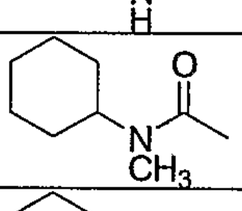
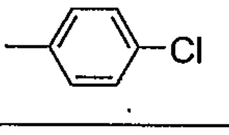
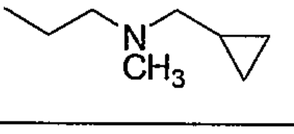
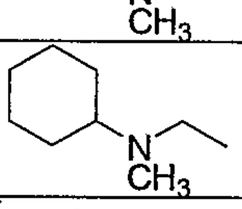
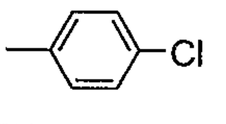
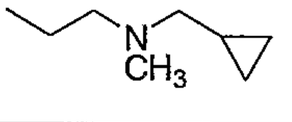
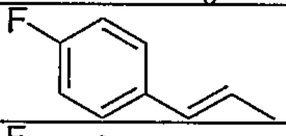
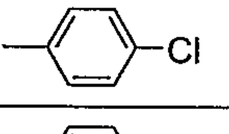
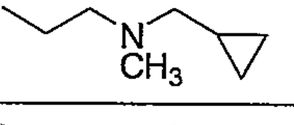
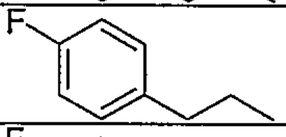
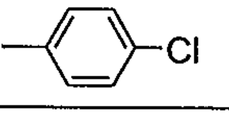
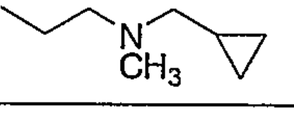
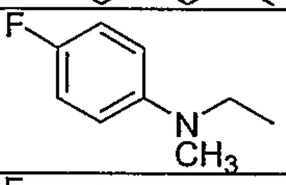
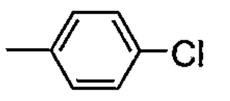
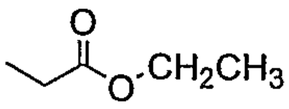
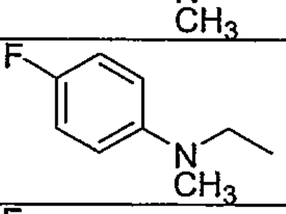
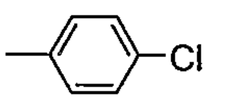
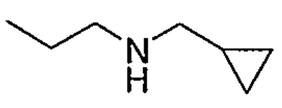
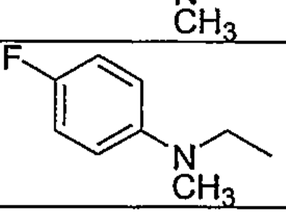
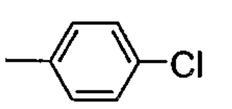
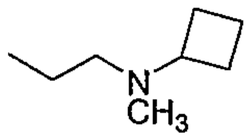
Representative compounds useful in the compositions and methods are delineated herein:

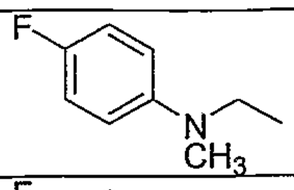
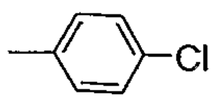
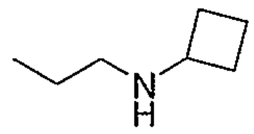
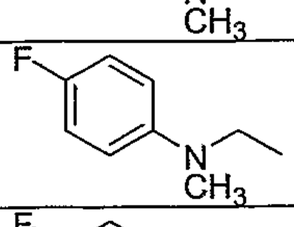
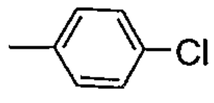
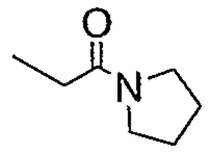
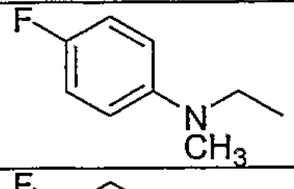
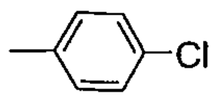
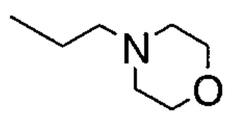
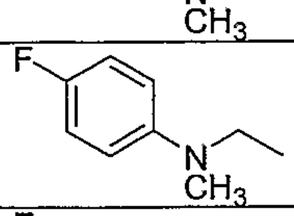
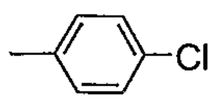
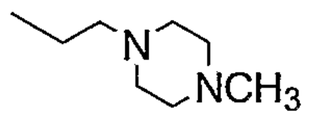
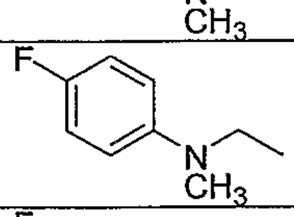
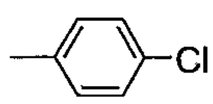
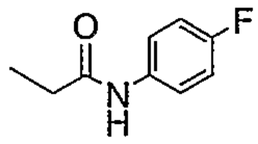
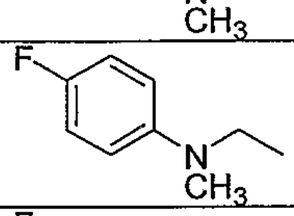
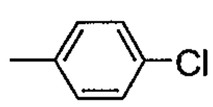
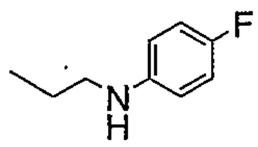
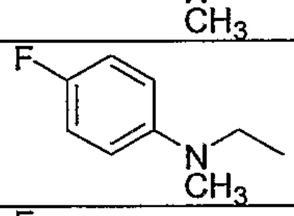
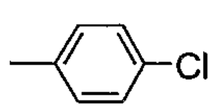
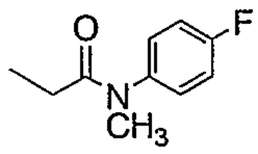
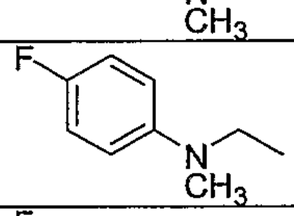
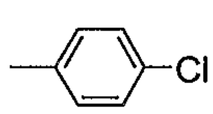
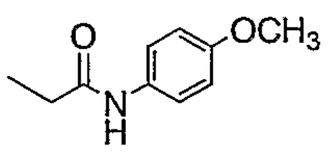
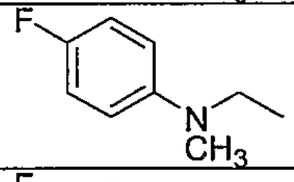
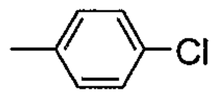
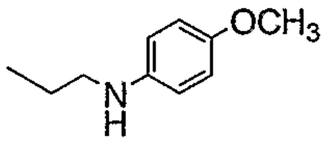
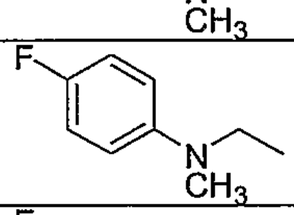
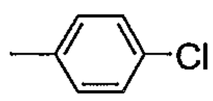
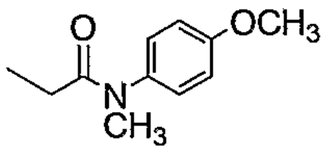
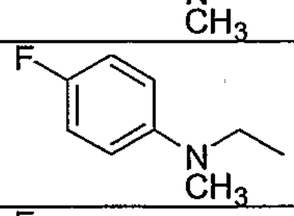
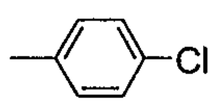
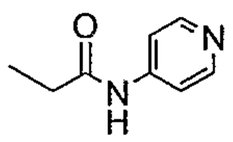
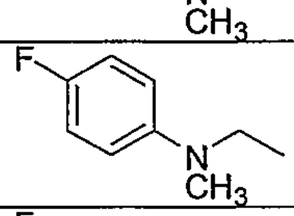
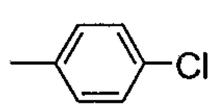
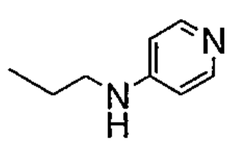
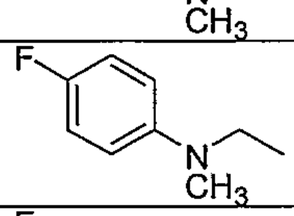
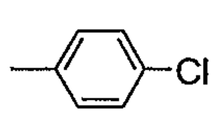
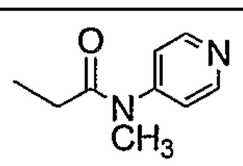
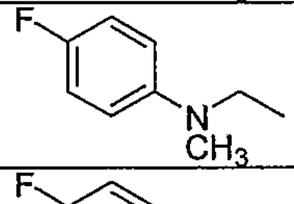
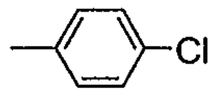
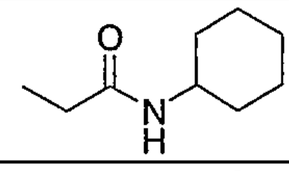
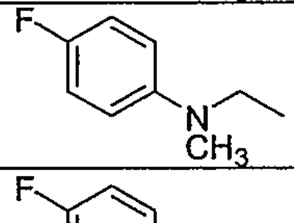
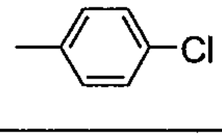
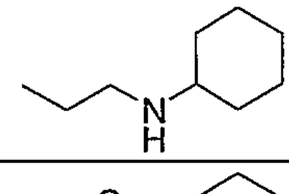
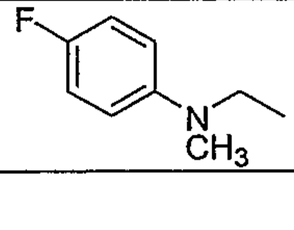
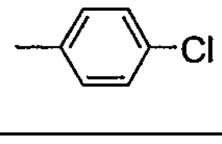
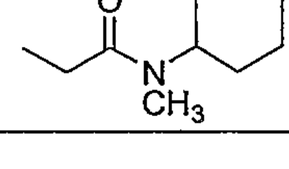
TABLE A1A

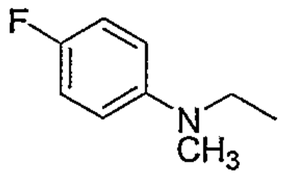
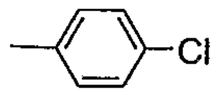
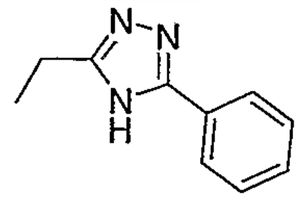
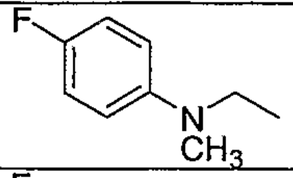
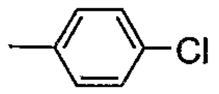
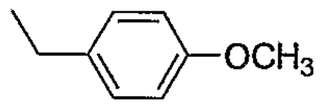
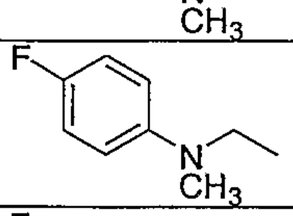
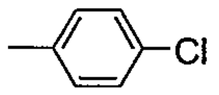
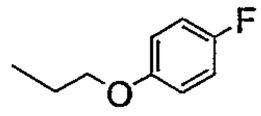
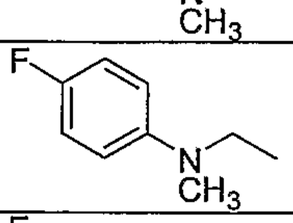
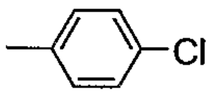
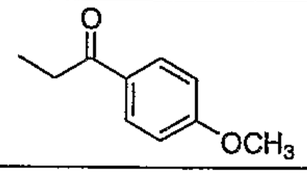
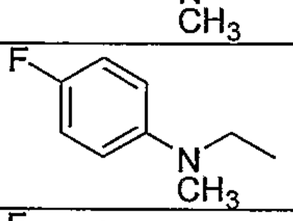
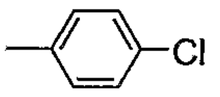
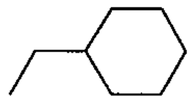
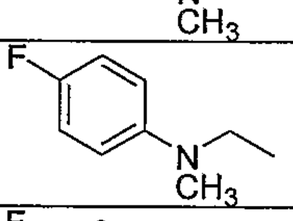
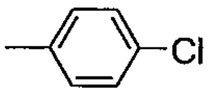
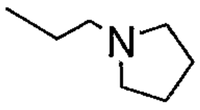
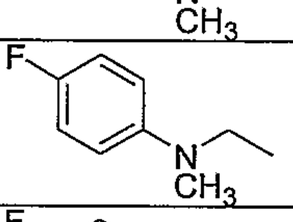
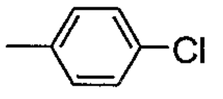
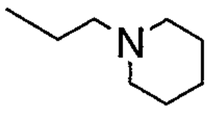
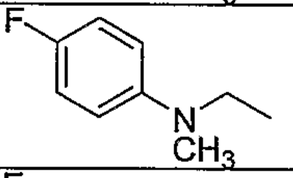
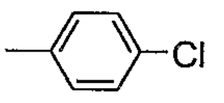
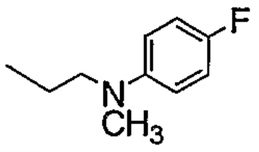
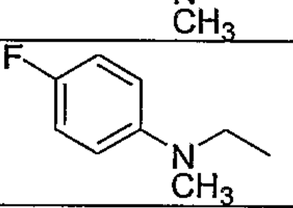
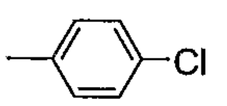
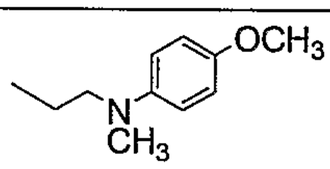
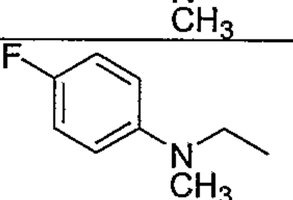
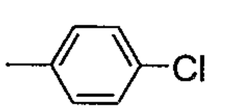
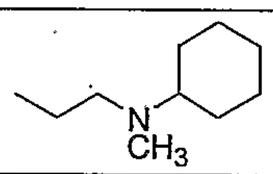
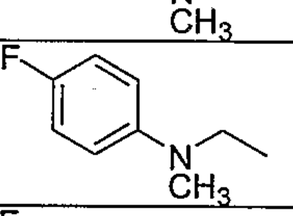
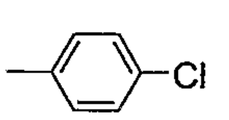
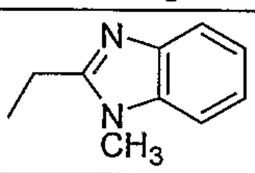
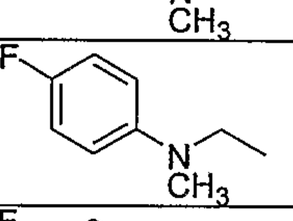
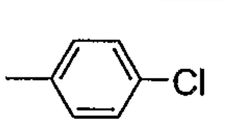
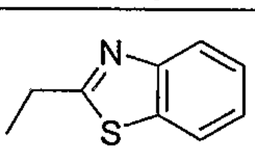
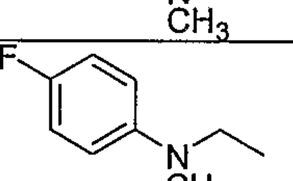
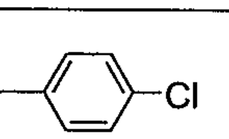
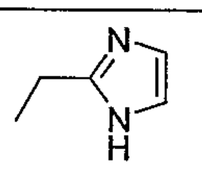
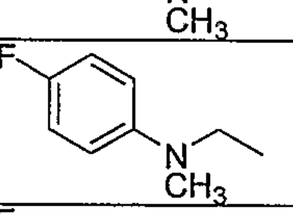
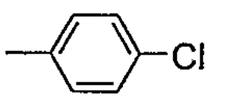
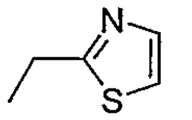
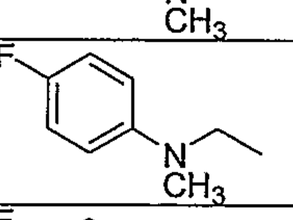
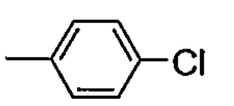
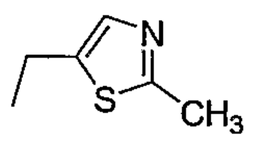
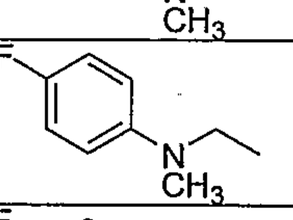
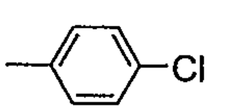
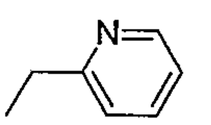
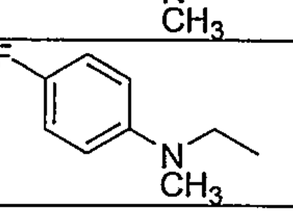
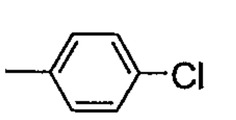
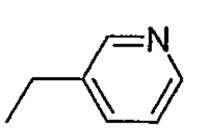


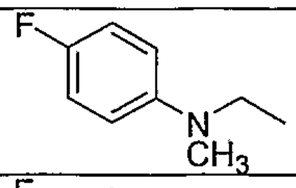
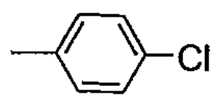
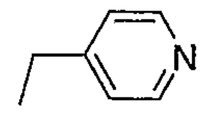
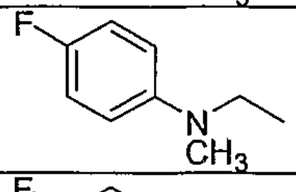
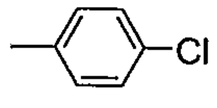
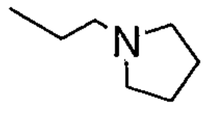
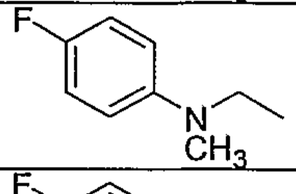
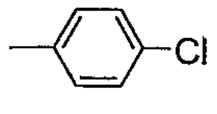
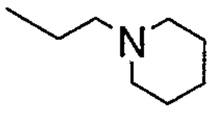
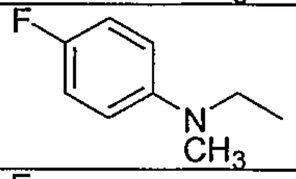
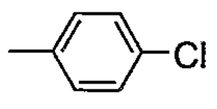
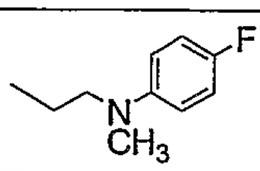
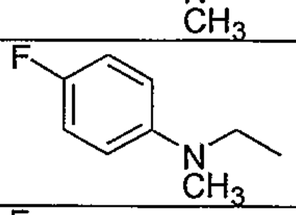
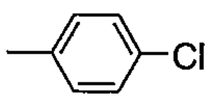
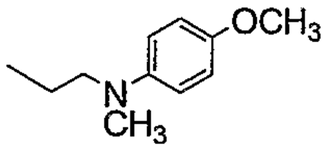
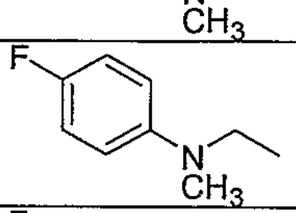
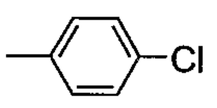
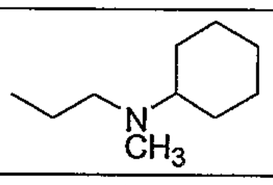
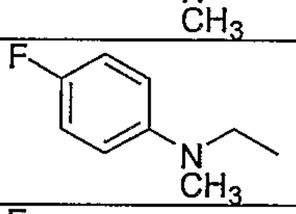
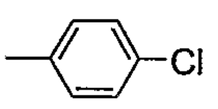
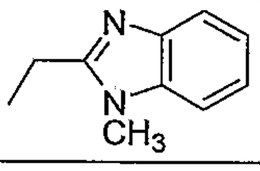
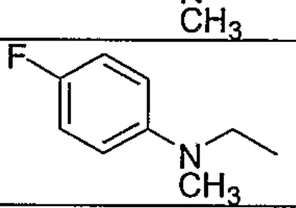
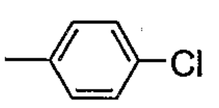
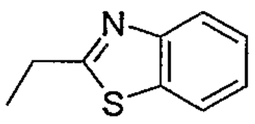
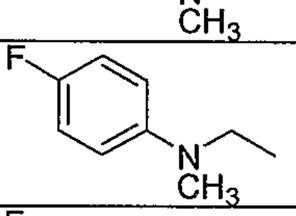
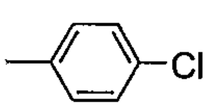
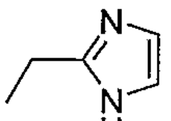
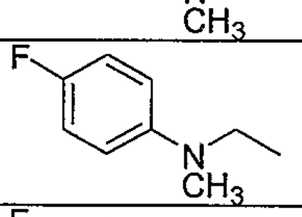
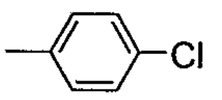
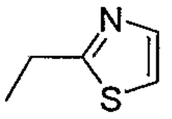
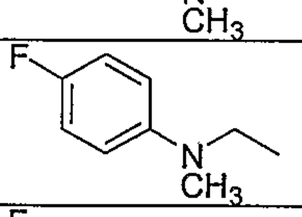
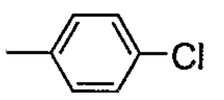
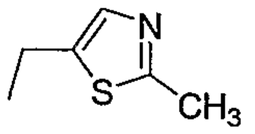
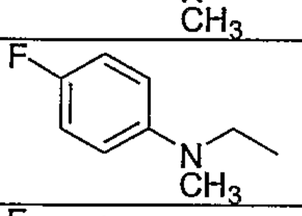
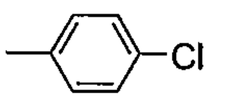
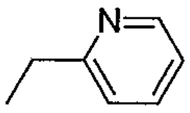
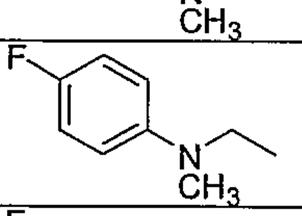
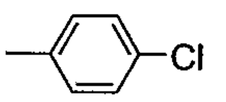
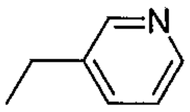
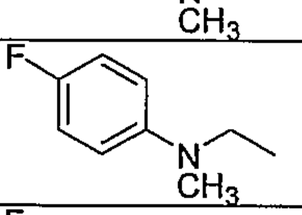
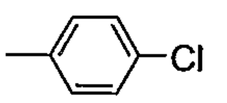
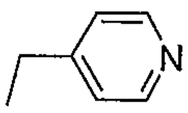
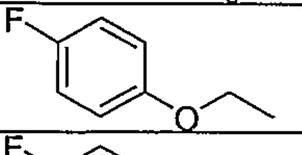
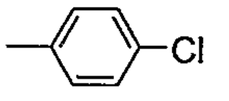
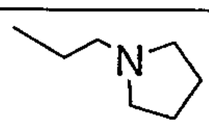
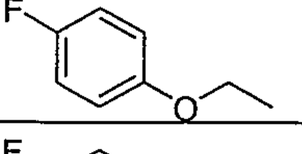
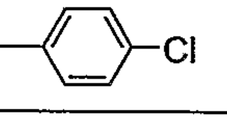
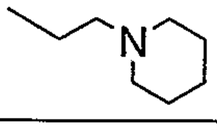
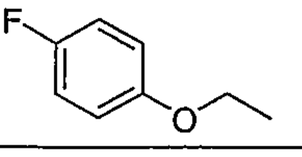
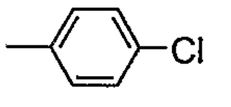
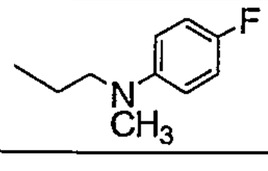
Cpd. No.	Ar^1-X-Y	R^1	R^2
A1			
A2			
A3			
A4			
A5			
A6			
A7			
A8			
A9			
A10			
A11			
A12			
A13			
A14			

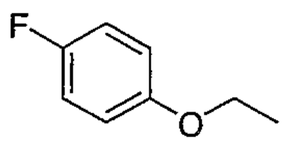
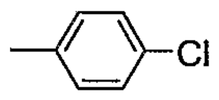
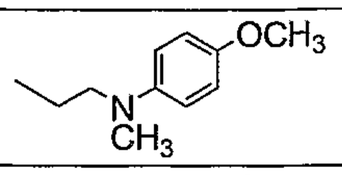
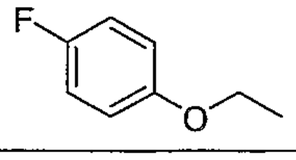
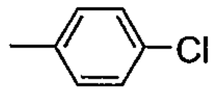
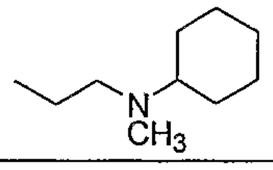
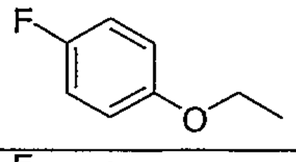
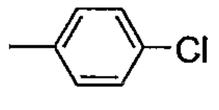
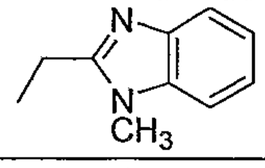
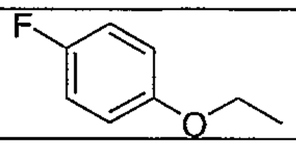
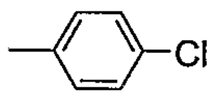
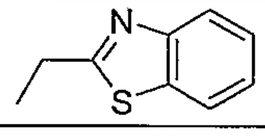
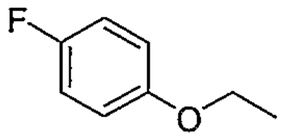
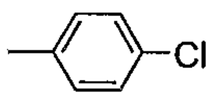
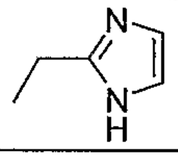
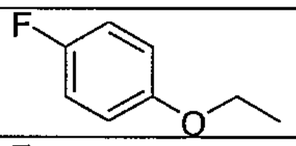
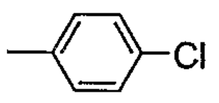
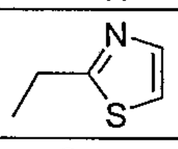
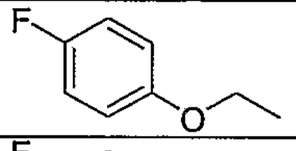
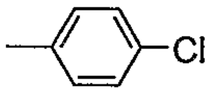
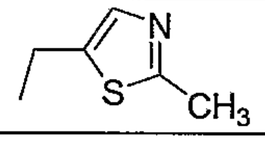
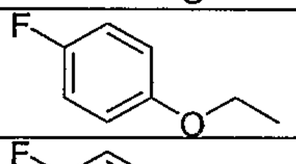
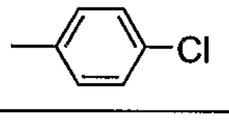
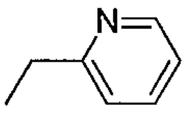
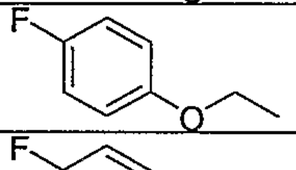
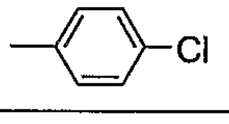
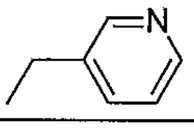
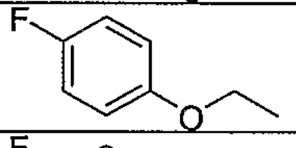
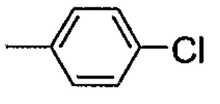
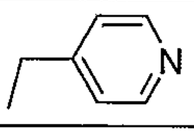
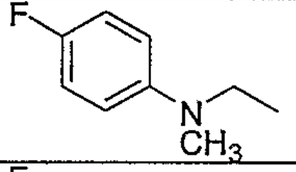
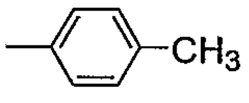
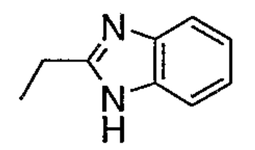
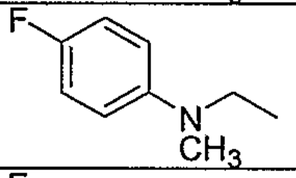
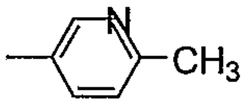
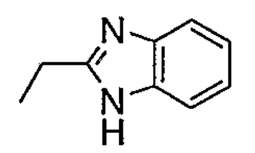
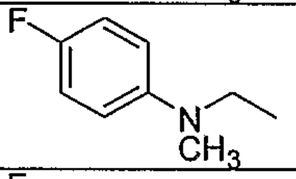
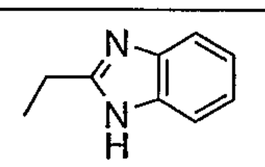
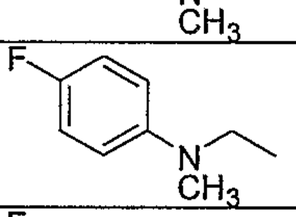
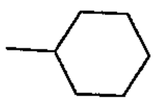
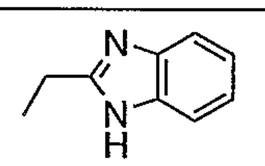
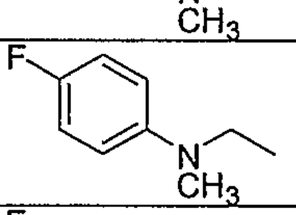
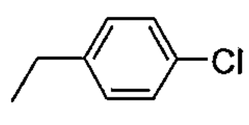
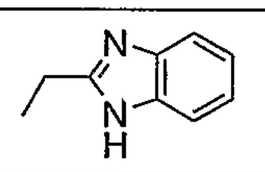
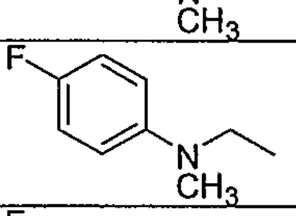
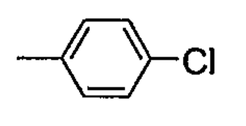
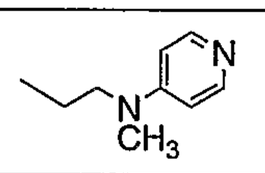
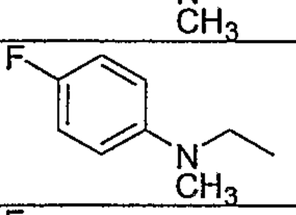
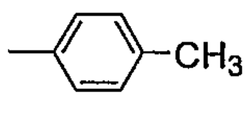
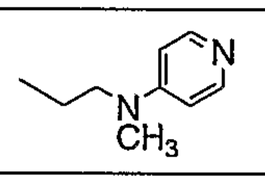
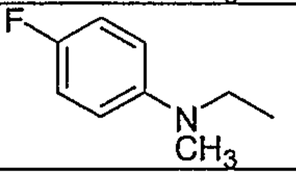
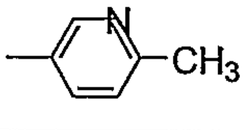
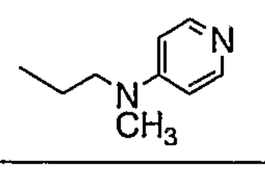
A15			
A16			
A17			
A18			
A19			
A20			
A21			
A22			
A23			
A24			
A25			
A26			
A27			
A28			
A29			
A30			
A31			
A32			

A33			
A34			
A35			
A36			
A37			
A38			
A39			
A40			
A41			
A42			
A43			
A44			
A45			
A46			
A47			
A48			
A49			
A50			

A51			
A52			
A53			
A54			
A55			
A56			
A57			
A58			
A59			
A60			
A61			
A62			
A63			
A64			
A65			
A66			

A67			
A68			
A69			
A70			
A71			
A72			
A73			
A74			
A75			
A76			
A77			
A78			
A79			
A80			
A81			
A82			
A83			

A84			
A85			
A86			
A87			
A88			
A89			
A90			
A91			
A92			
A93			
A94			
A95			
A96			
A97			
A98			
A99			
A100			

A101			
A102			
A103			
A104			
A105			
A106			
A107			
A108			
A109			
A110			
A111			
A112			
A113		CH_3	
A114			
A115			
A116			
A117			
A118			

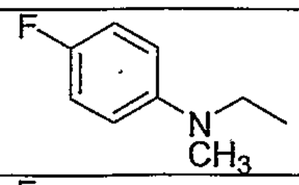
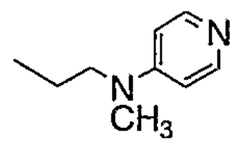
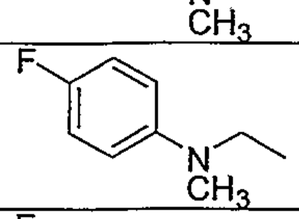
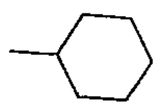
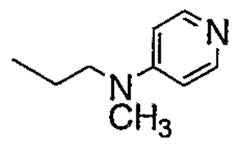
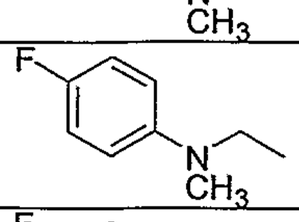
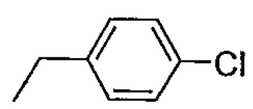
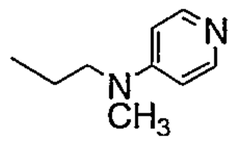
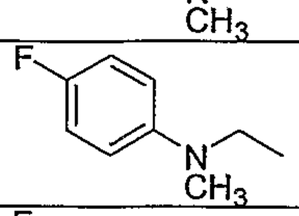
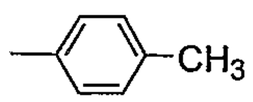
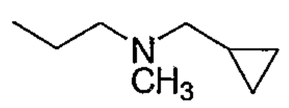
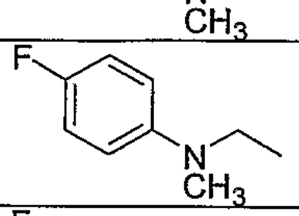
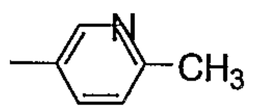
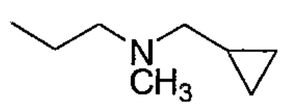
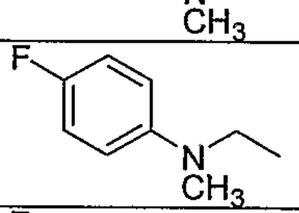
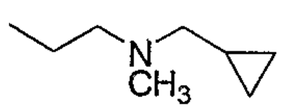
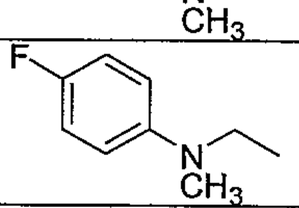
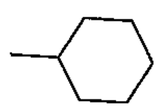
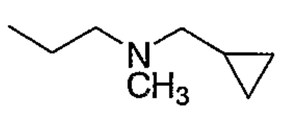
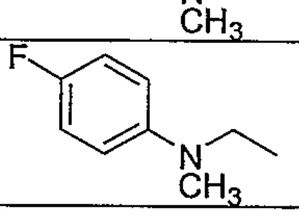
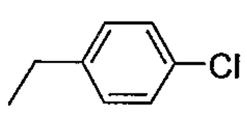
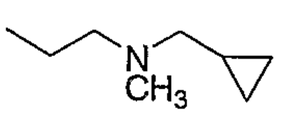
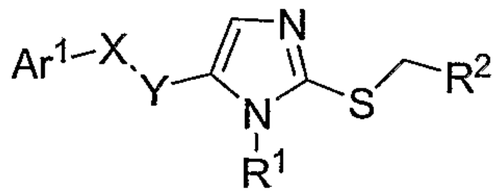
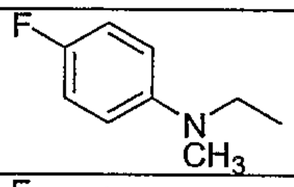
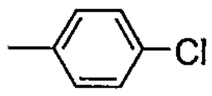
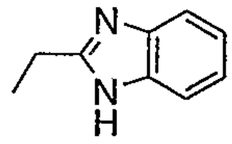
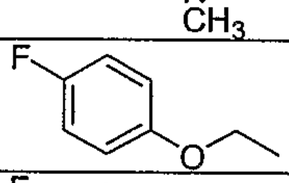
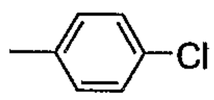
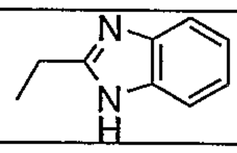
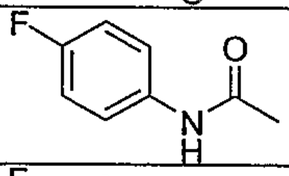
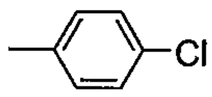
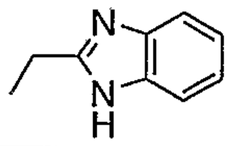
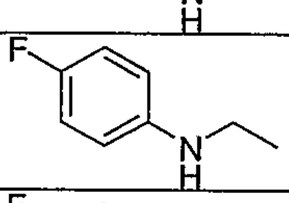
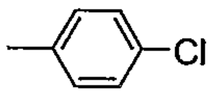
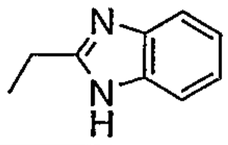
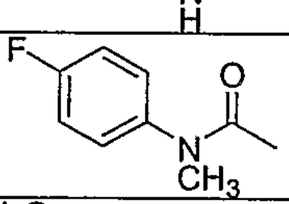
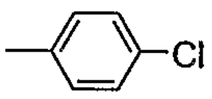
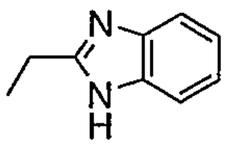
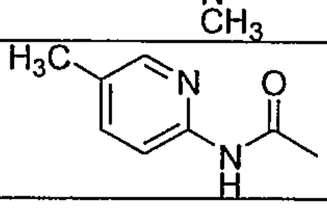
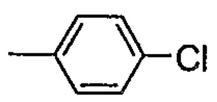
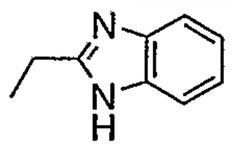
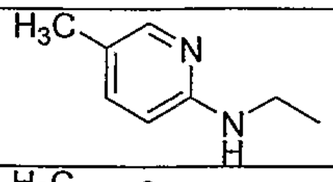
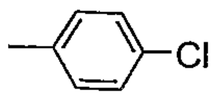
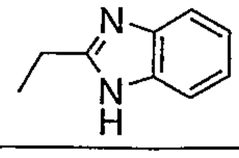
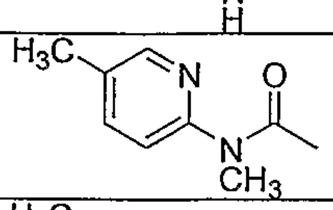
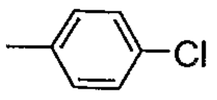
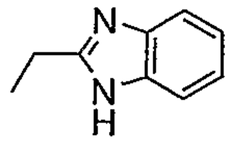
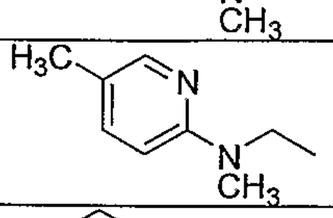
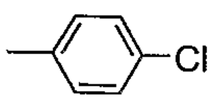
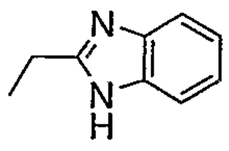
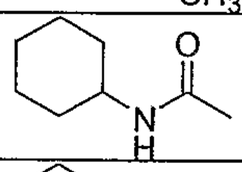
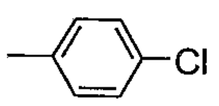
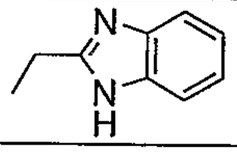
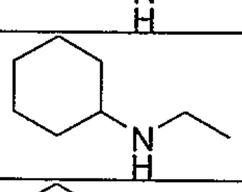
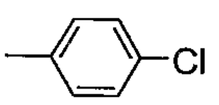
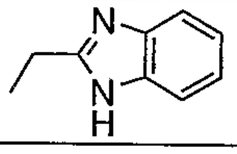
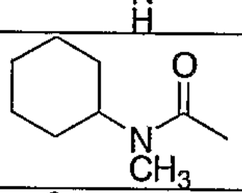
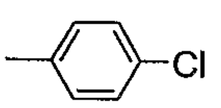
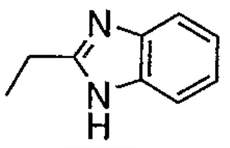
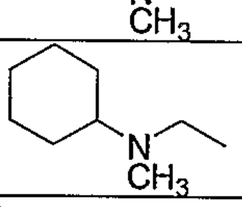
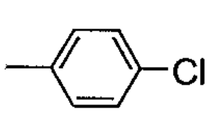
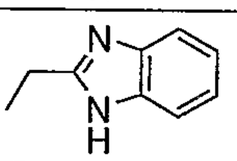
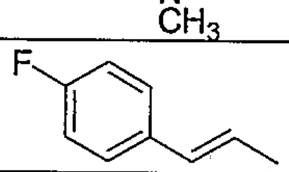
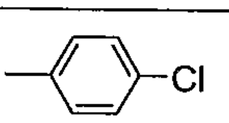
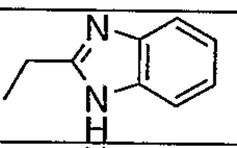
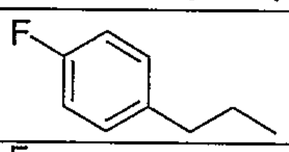
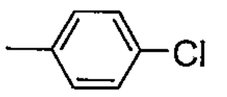
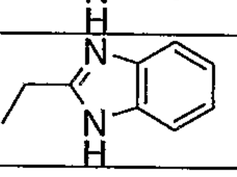
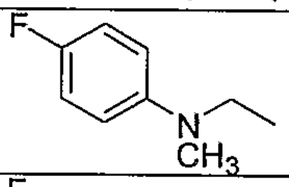
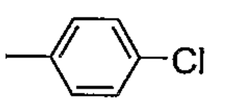
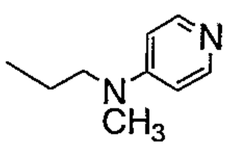
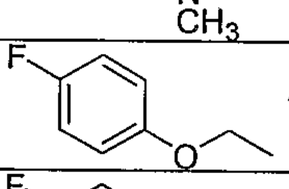
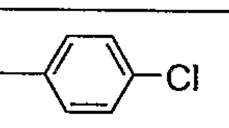
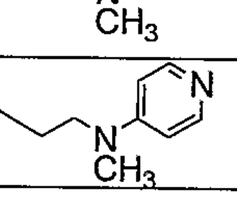
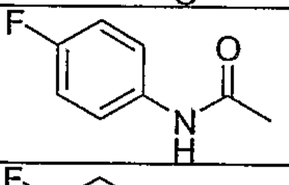
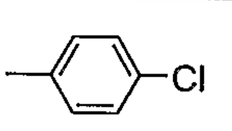
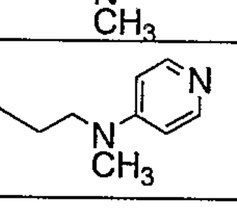
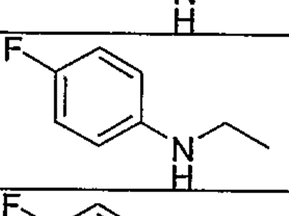
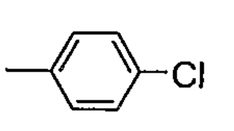
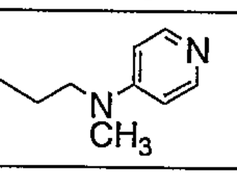
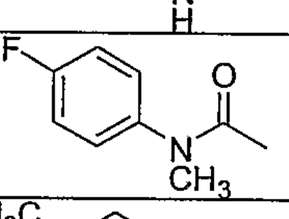
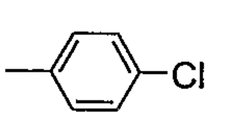
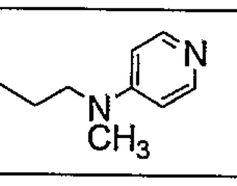
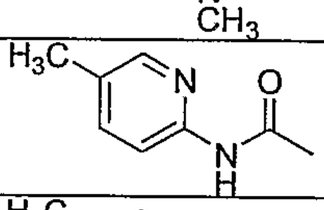
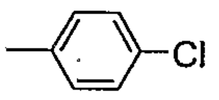
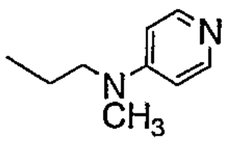
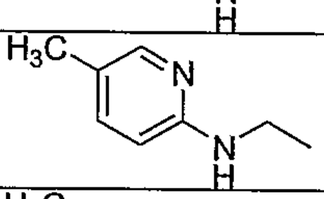
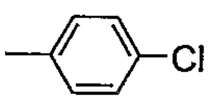
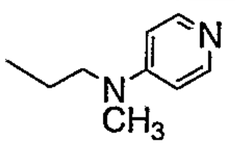
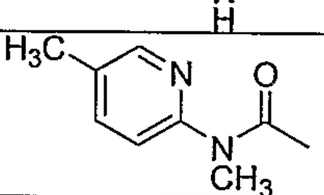
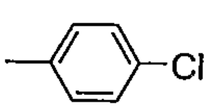
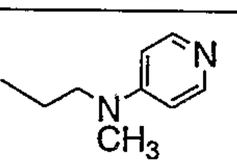
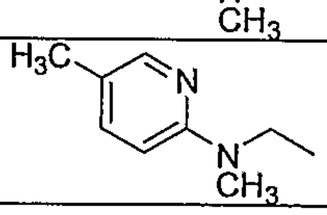
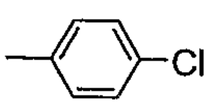
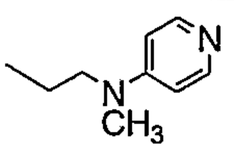
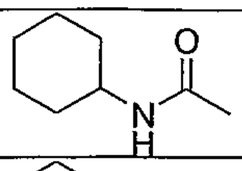
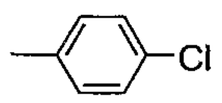
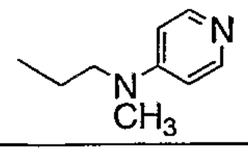
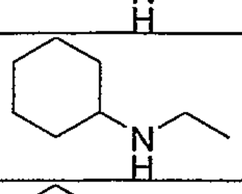
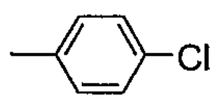
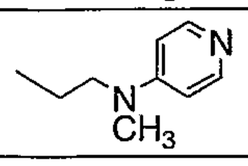
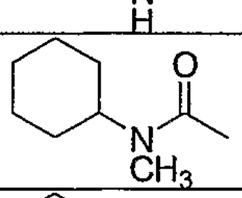
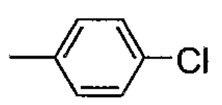
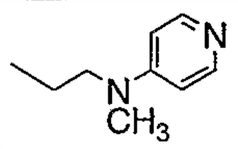
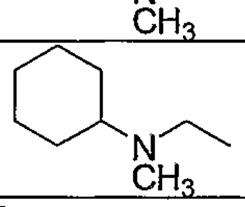
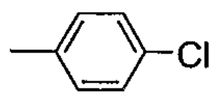
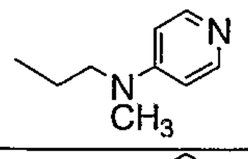
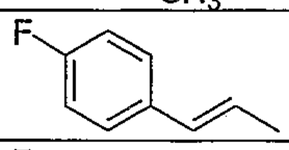
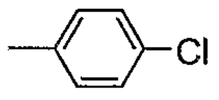
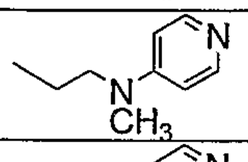
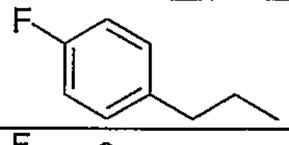
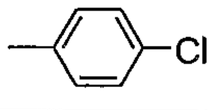
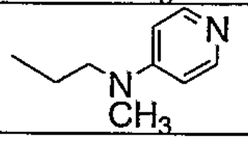
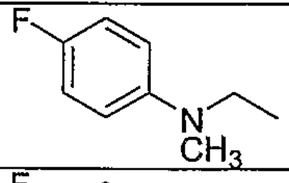
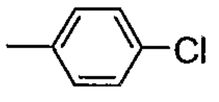
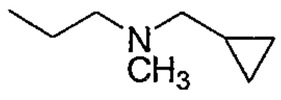
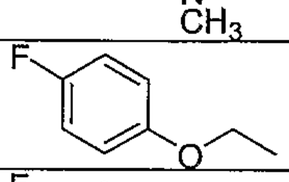
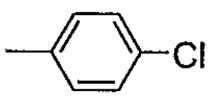
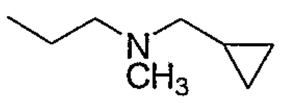
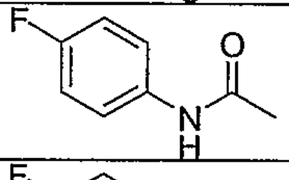
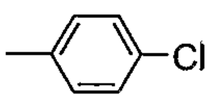
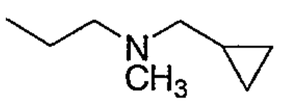
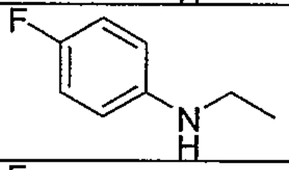
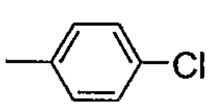
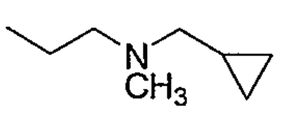
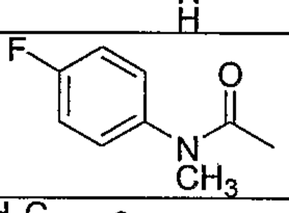
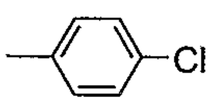
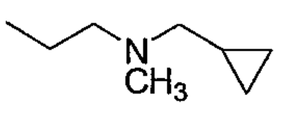
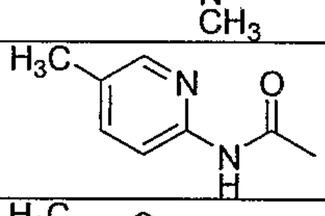
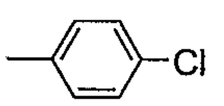
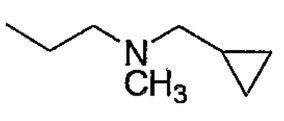
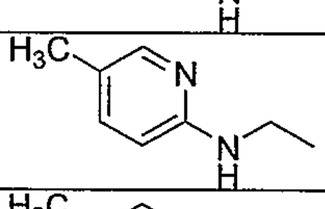
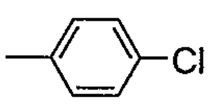
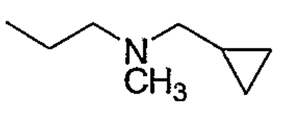
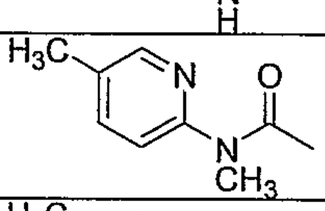
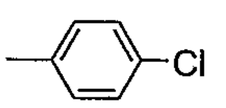
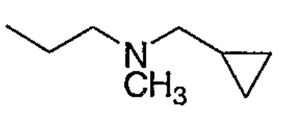
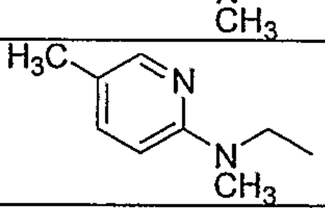
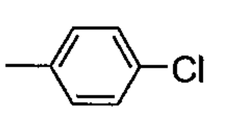
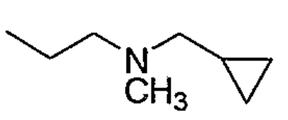
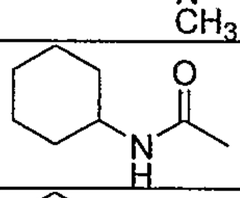
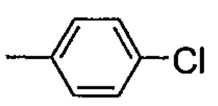
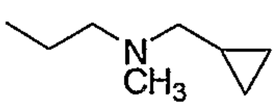
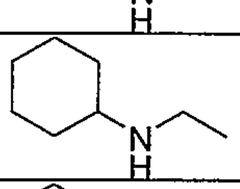
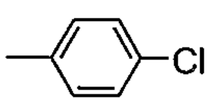
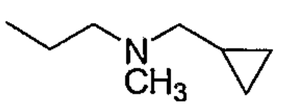
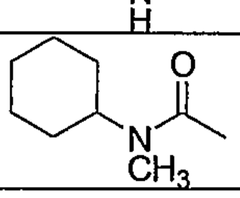
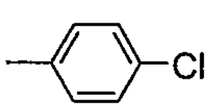
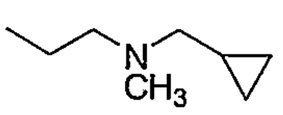
A119		CH_3	
A120			
A121			
A122			
A123			
A124		CH_3	
A125			
A126			

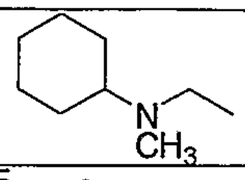
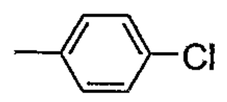
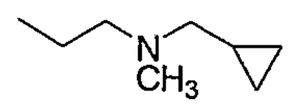
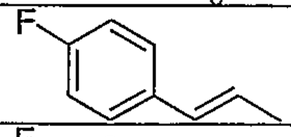
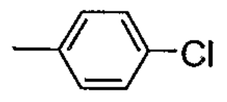
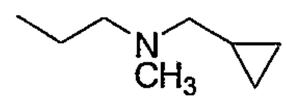
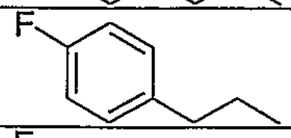
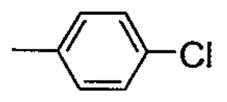
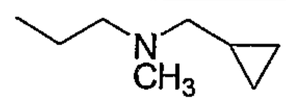
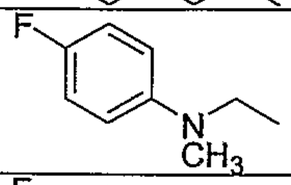
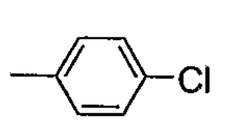
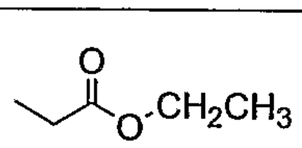
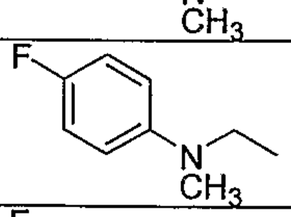
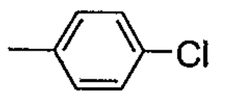
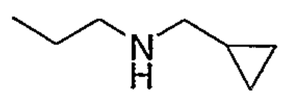
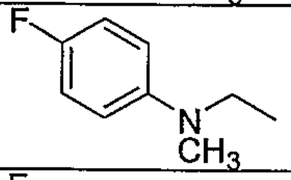
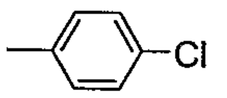
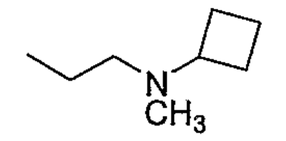
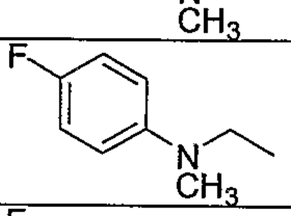
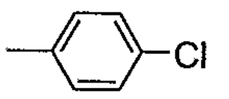
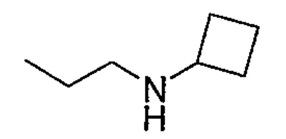
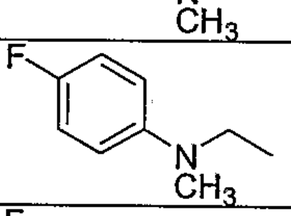
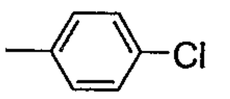
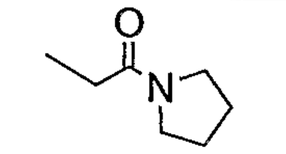
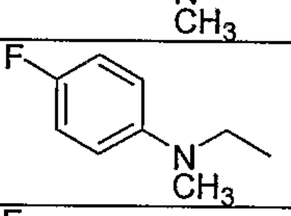
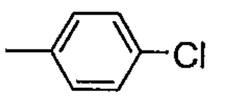
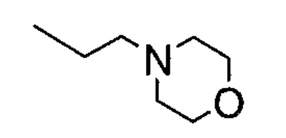
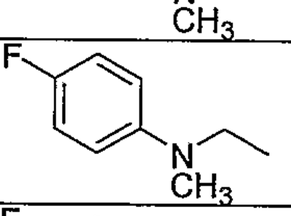
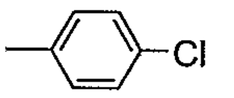
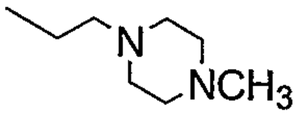
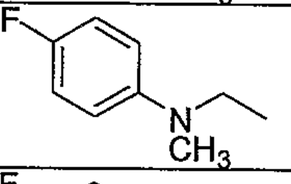
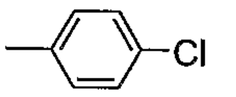
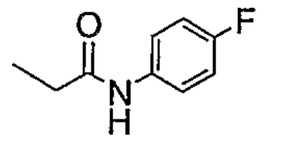
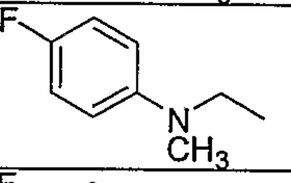
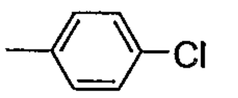
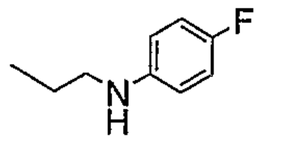
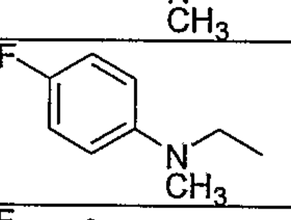
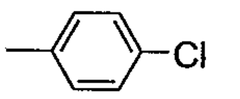
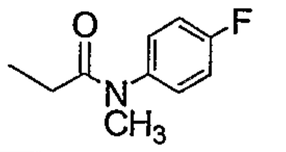
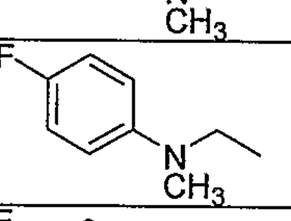
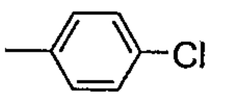
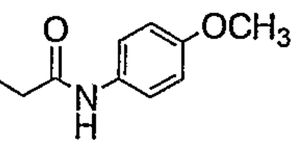
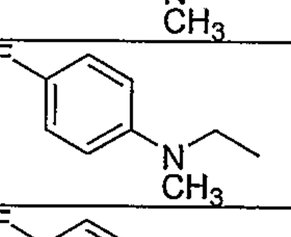
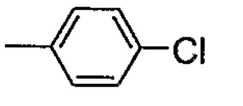
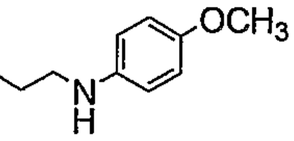
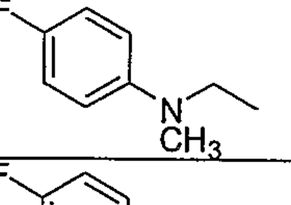
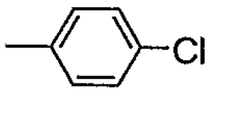
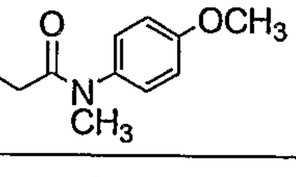
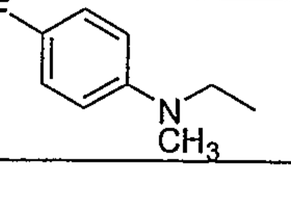
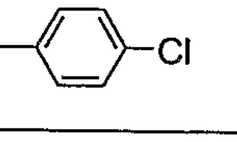
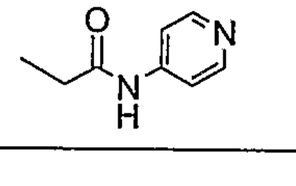
TABLE A1B

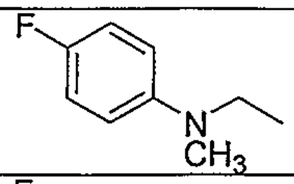
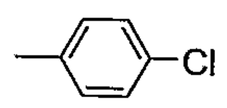
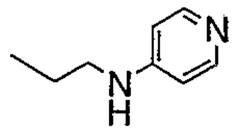
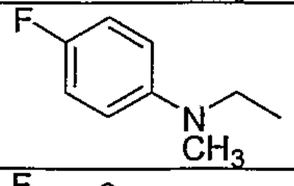
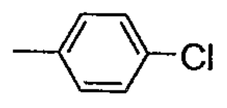
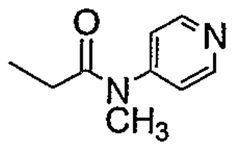
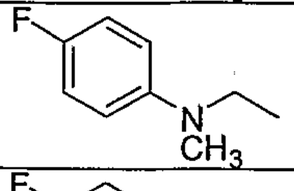
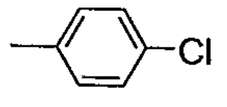
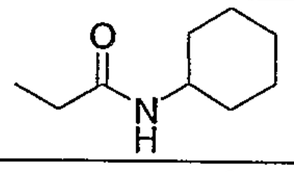
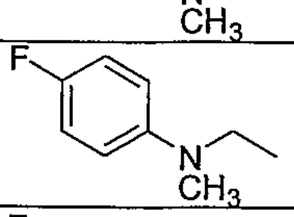
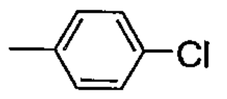
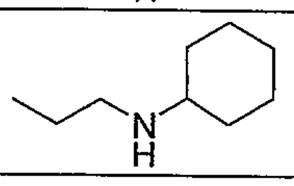
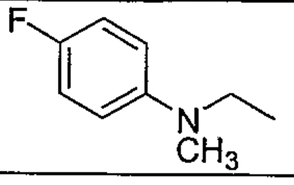
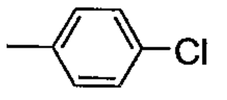
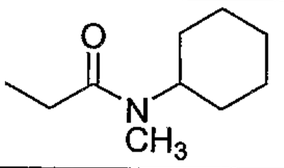
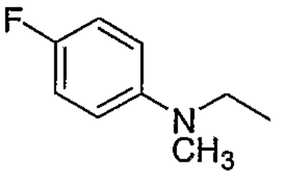
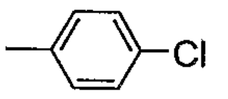
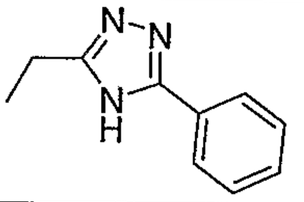
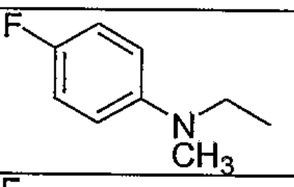
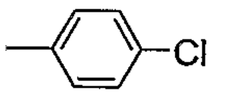
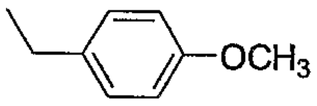
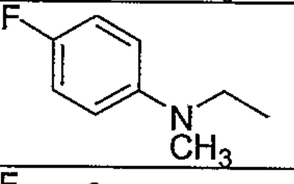
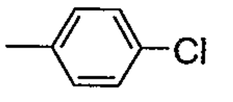
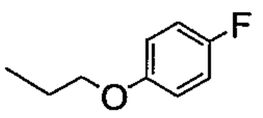
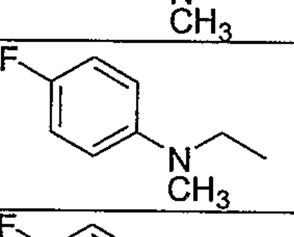
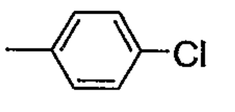
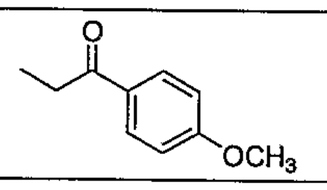
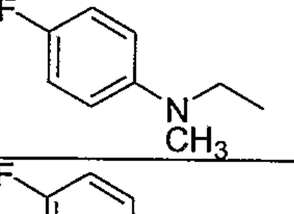
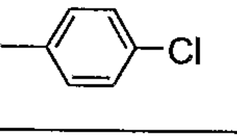
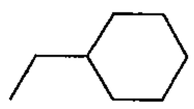
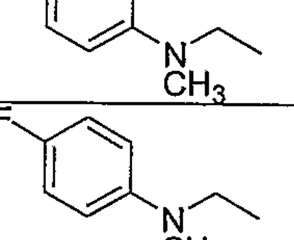
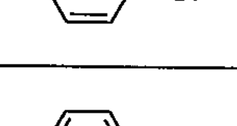
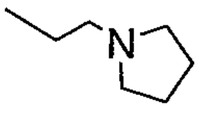
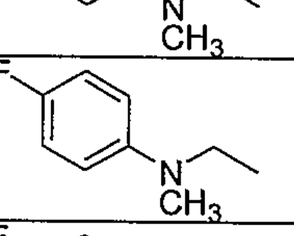
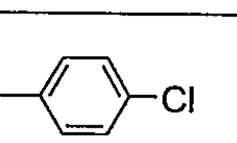
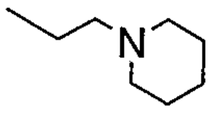
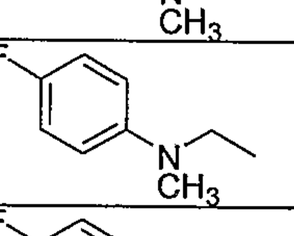
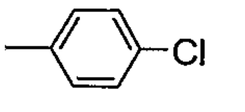
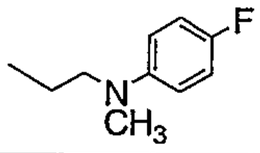
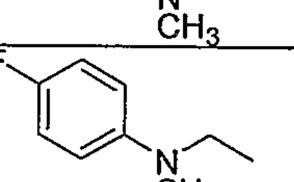
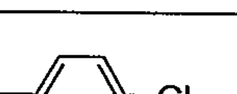
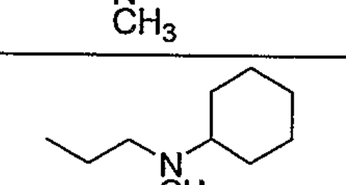
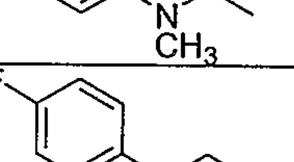
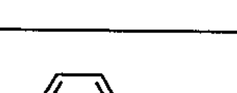
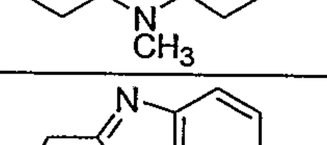
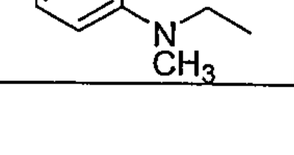
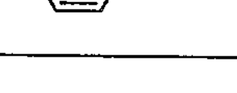
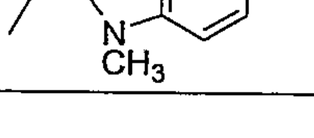


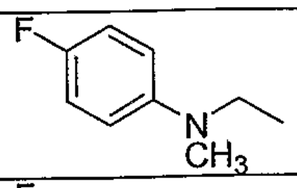
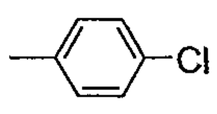
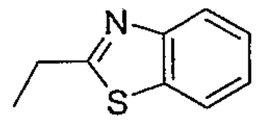
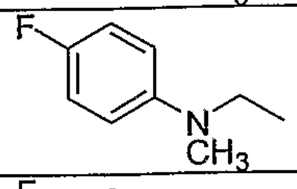
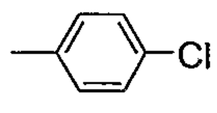
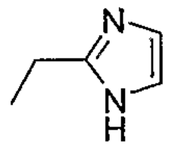
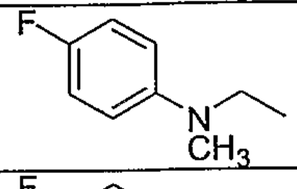
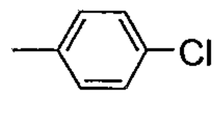
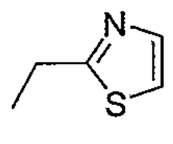
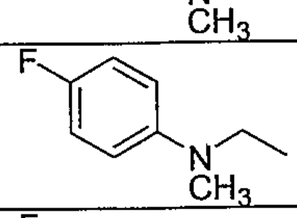
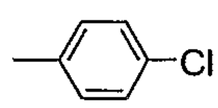
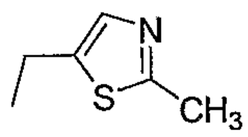
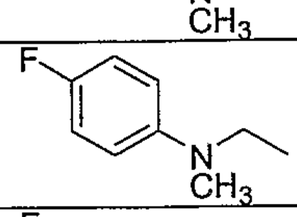
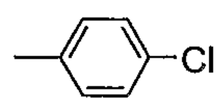
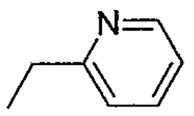
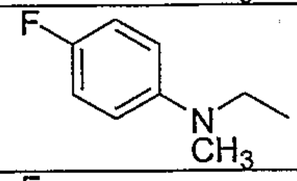
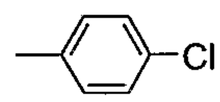
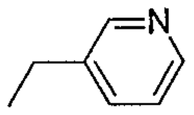
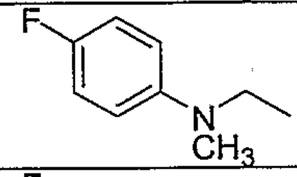
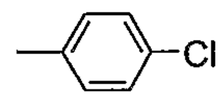
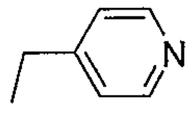
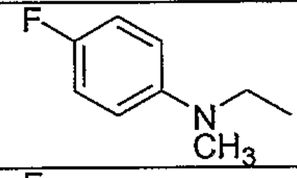
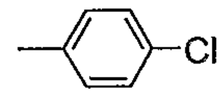
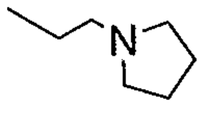
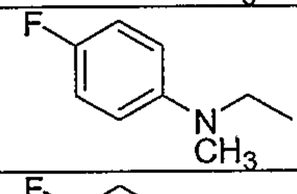
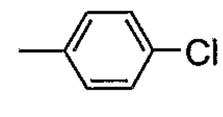
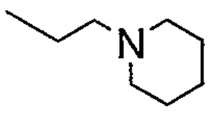
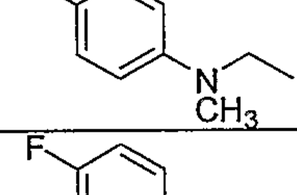
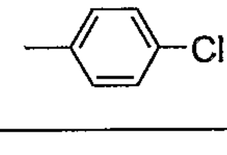
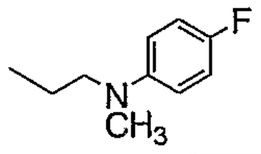
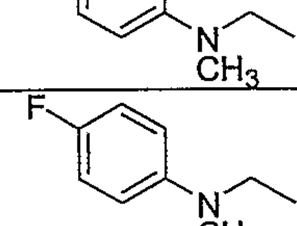
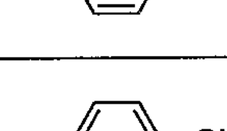
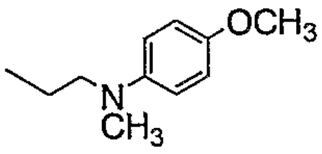
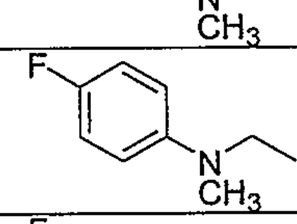
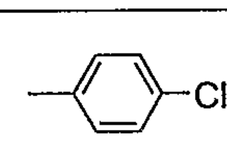
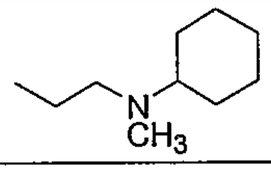
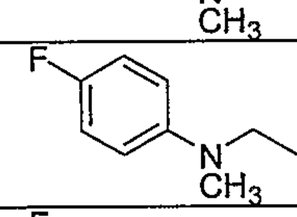
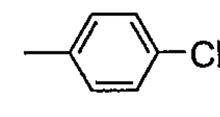
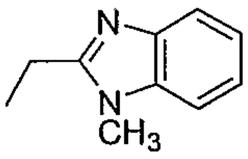
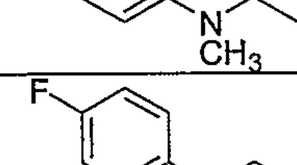
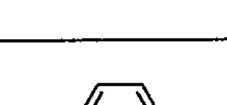
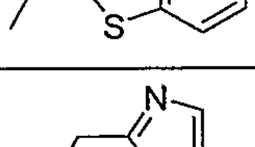
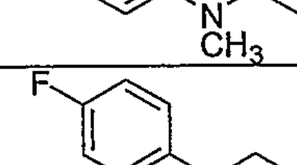
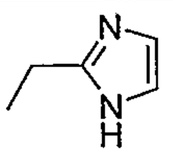
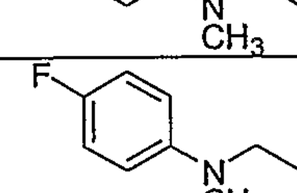
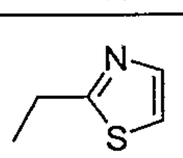
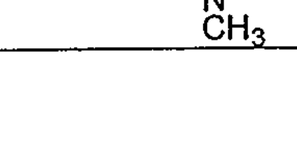
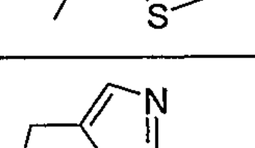
Cpd. No.	Ar^1-X-Y	R^1	R^2
A127			
A128			
A129			
A130			
A131			
A132			

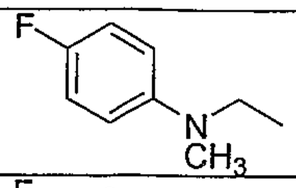
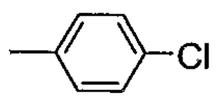
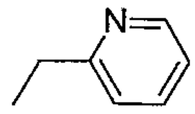
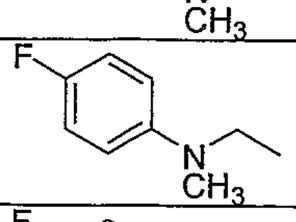
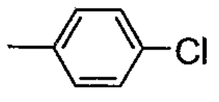
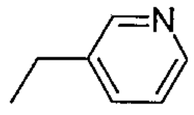
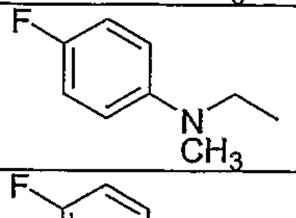
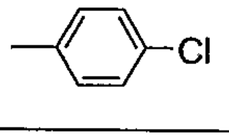
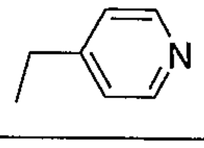
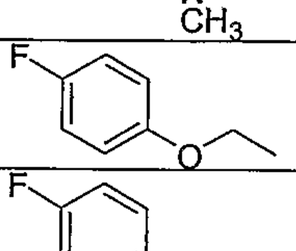
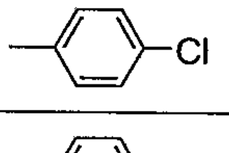
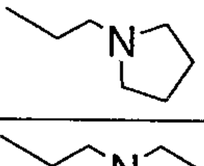
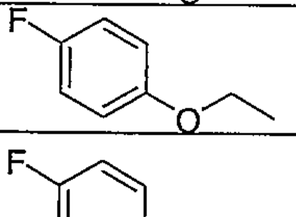
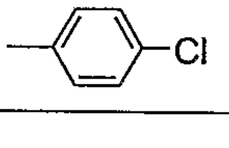
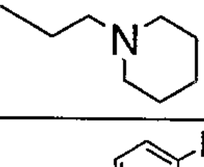
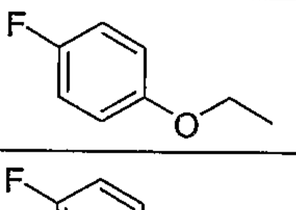
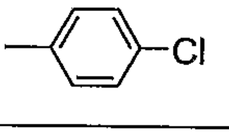
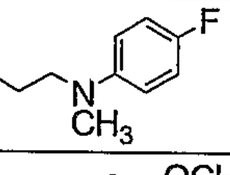
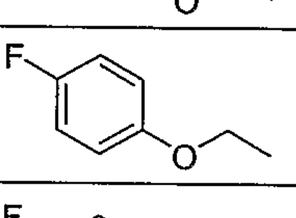
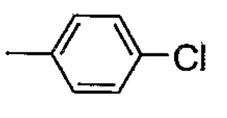
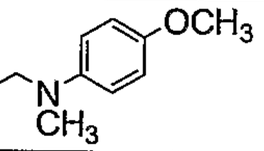
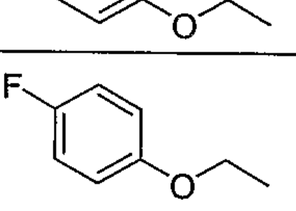
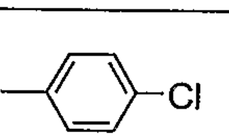
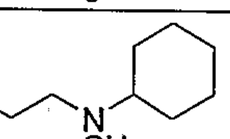
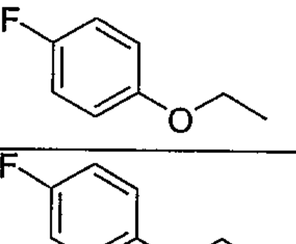
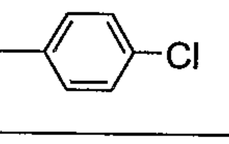
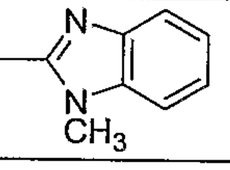
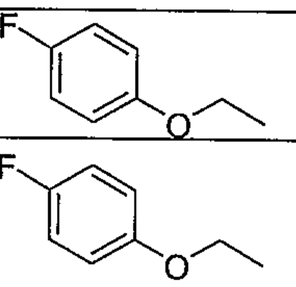
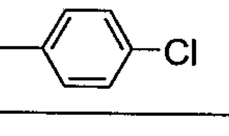
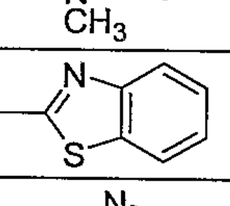
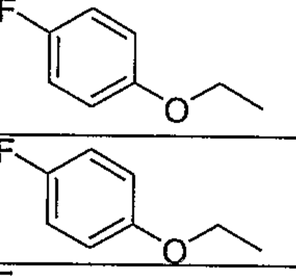
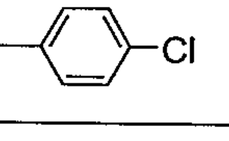
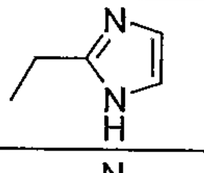
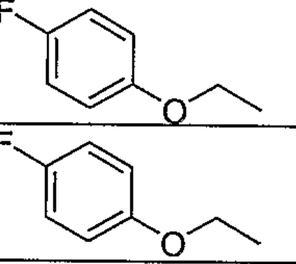
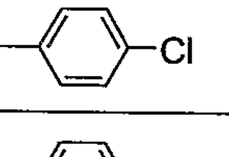
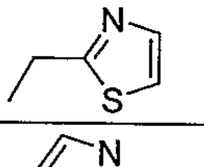
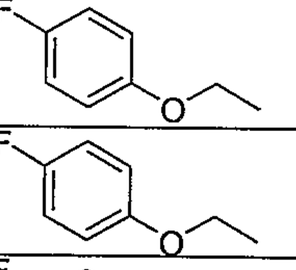
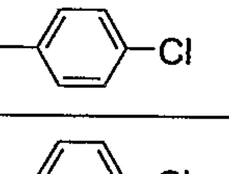
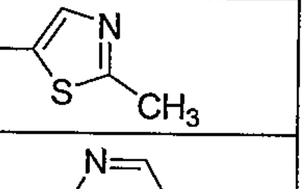
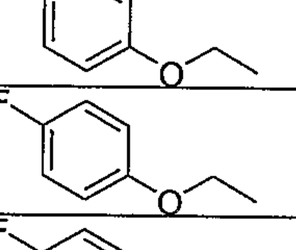
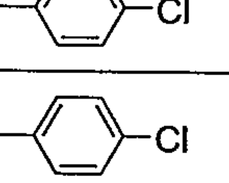
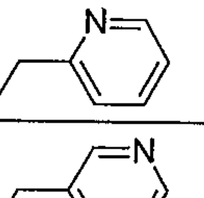
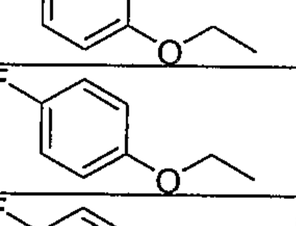
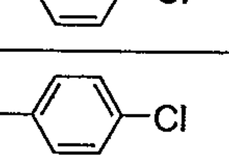
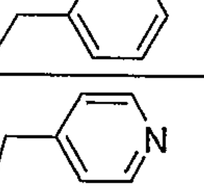
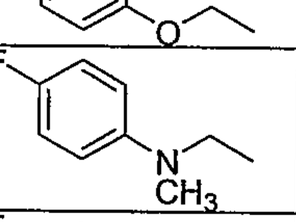
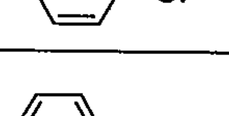
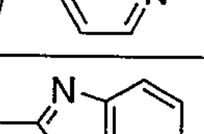
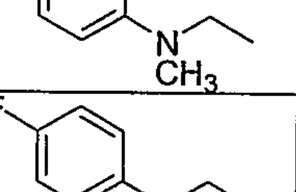
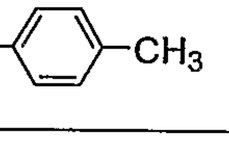
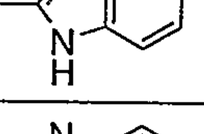
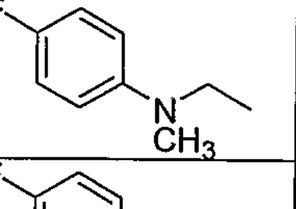
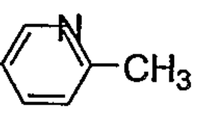
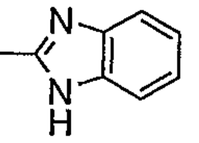
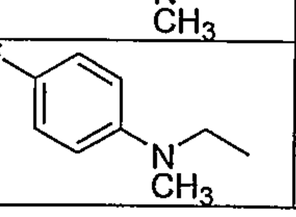
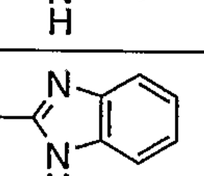
A133			
A134			
A135			
A136			
A137			
A138			
A139			
A140			
A141			
A142			
A143			
A144			
A145			
A146			
A147			
A148			
A149			
A150			

A151			
A152			
A153			
A154			
A155			
A156			
A157			
A158			
A159			
A160			
A161			
A162			
A163			
A164			
A165			
A166			
A167			
A168			

A169			
A170			
A171			
A172			
A173			
A174			
A175			
A176			
A177			
A178			
A179			
A180			
A181			
A182			
A183			
A184			
A185			

A186			
A187			
A188			
A189			
A190			
A191			
A192			
A193			
A194			
A195			
A196			
A197			
A198			
A199			
A200			
A201			

A202			
A203			
A204			
A205			
A206			
A207			
A208			
A209			
A210			
A211			
A212			
A213			
A214			
A215			
A216			
A217			
A218			

A219			
A220			
A221			
A222			
A223			
A224			
A225			
A226			
A227			
A228			
A229			
A230			
A231			
A232			
A233			
A234			
A235			
A236			
A237		CH_3	

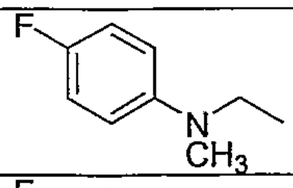
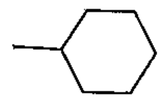
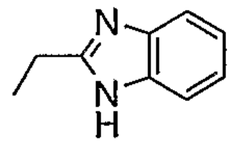
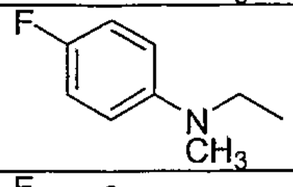
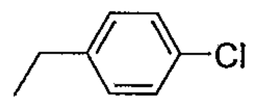
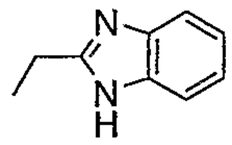
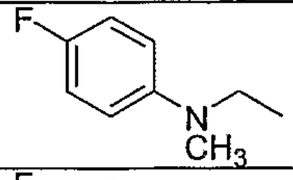
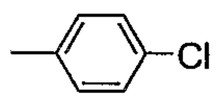
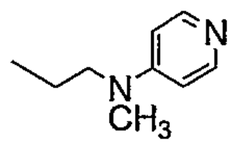
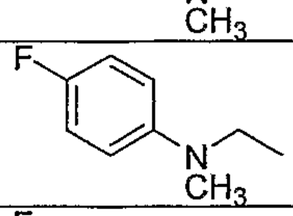
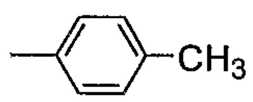
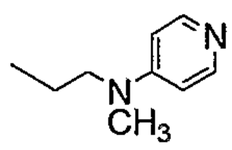
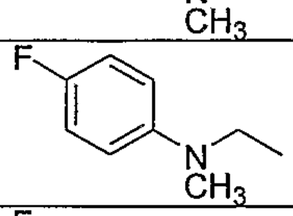
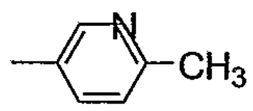
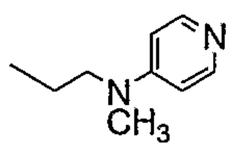
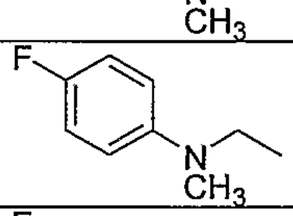
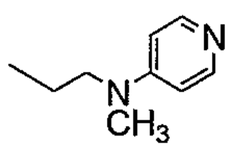
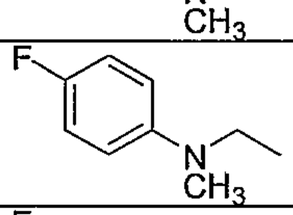
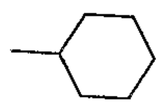
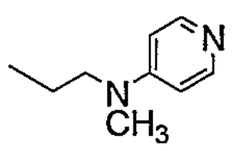
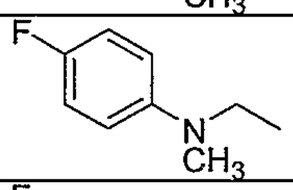
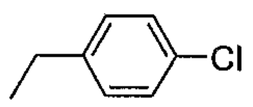
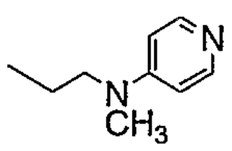
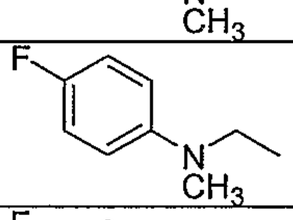
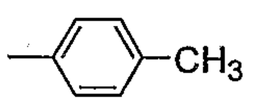
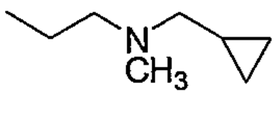
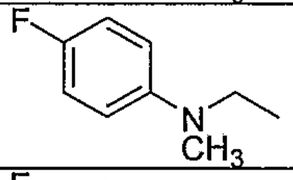
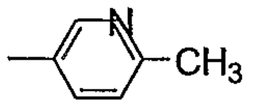
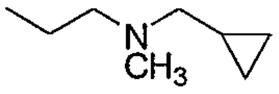
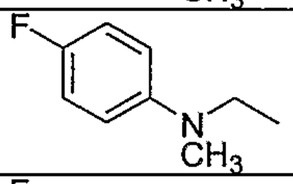
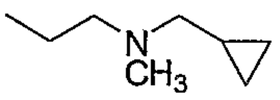
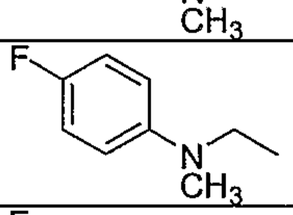
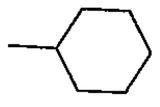
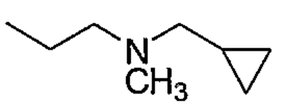
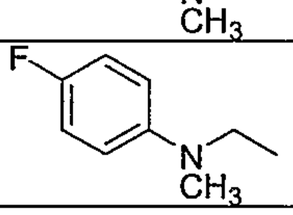
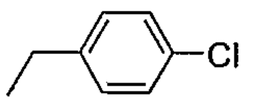
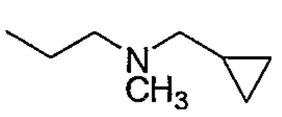
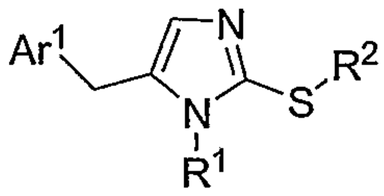
A238			
A239			
A240			
A241			
A242			
A243		CH_3	
A244			
A245			
A246			
A247			
A248		CH_3	
A249			
A250			

TABLE A1C



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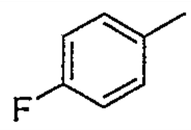
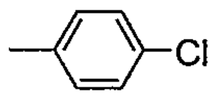
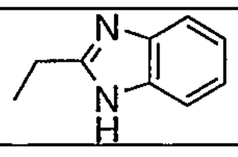
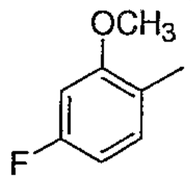
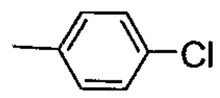
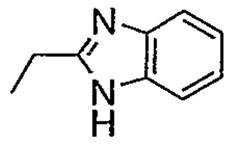
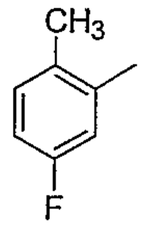
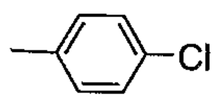
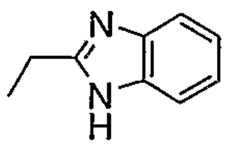
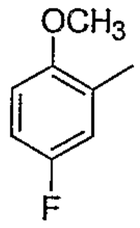
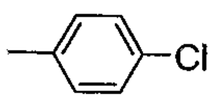
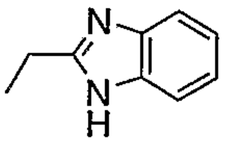
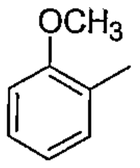
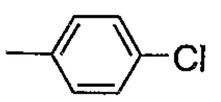
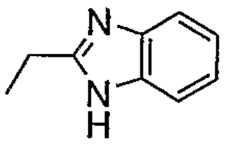
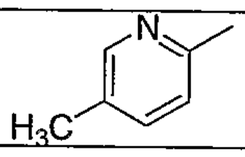
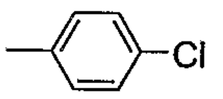
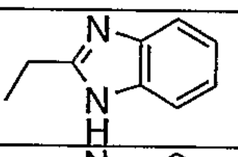
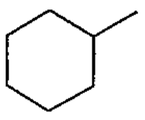
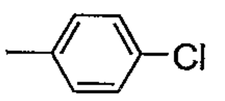
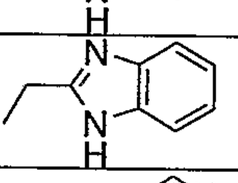
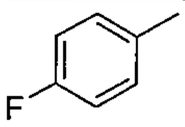
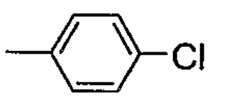
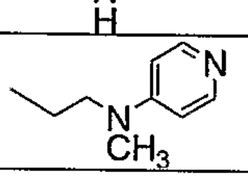
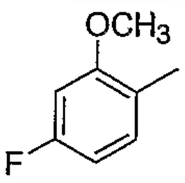
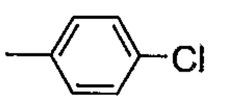
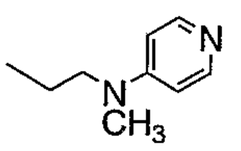
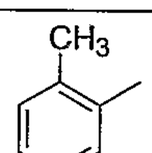
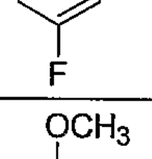
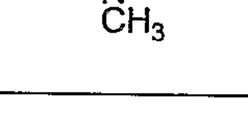
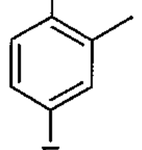
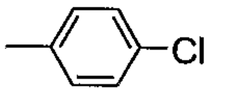
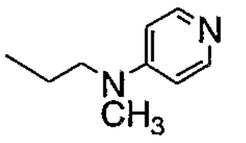
A251			

A252			
A253			
A254			
A255			
A256			
A257			
A258			
A259			
A260			
A261			
A262			
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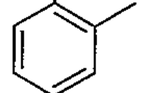
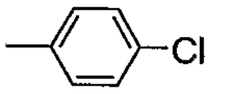
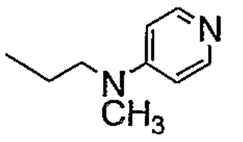
A264			
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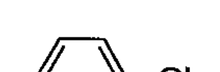
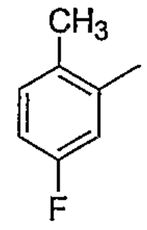
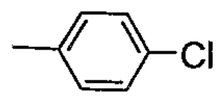
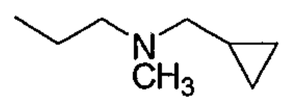
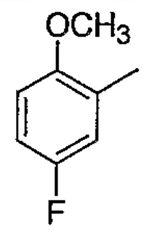
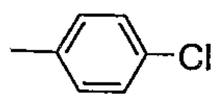
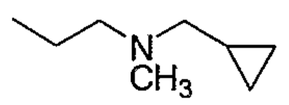
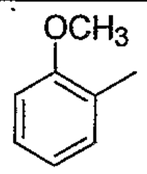
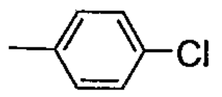
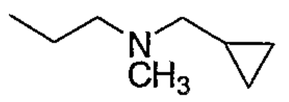
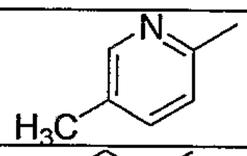
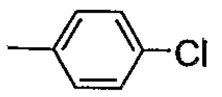
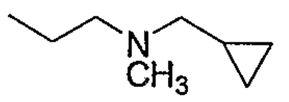
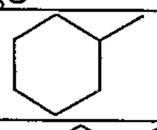
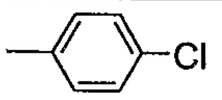
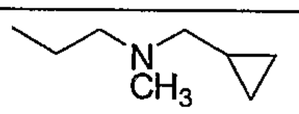
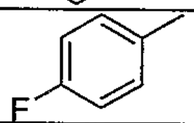
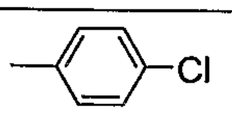
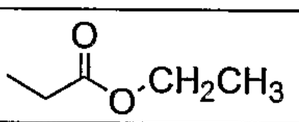
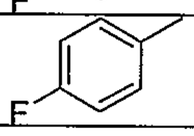
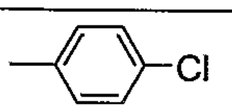
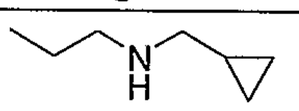
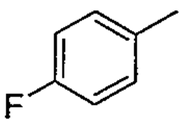
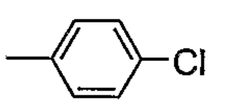
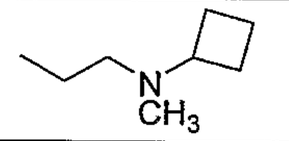
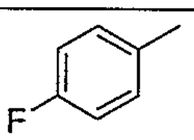
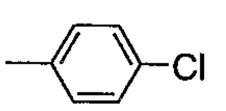
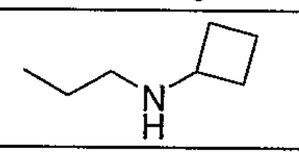
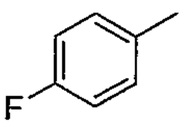
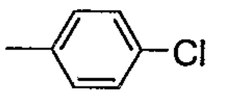
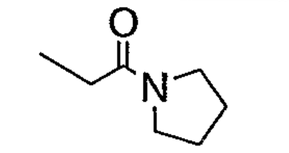
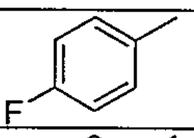
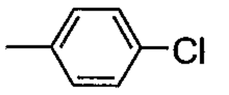
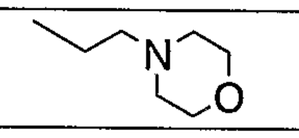
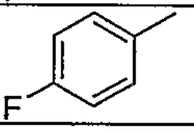
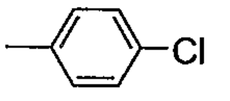
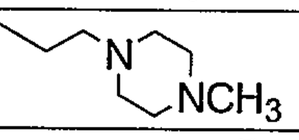
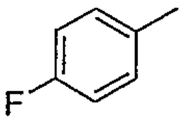
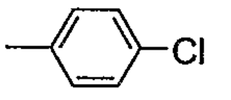
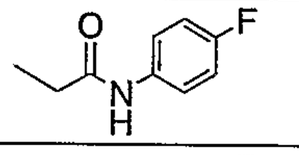
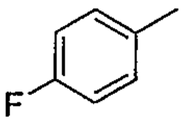
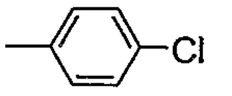
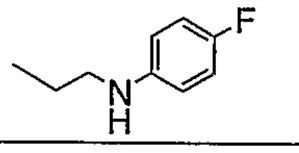
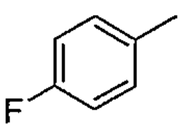
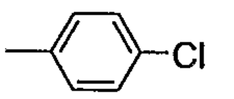
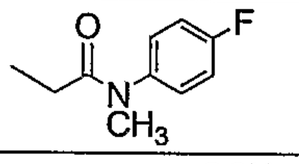
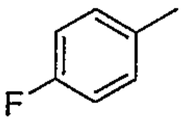
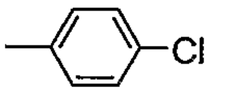
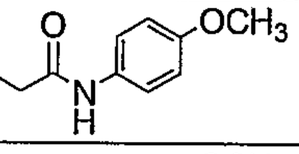
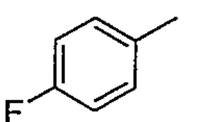
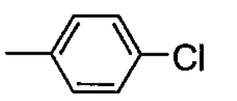
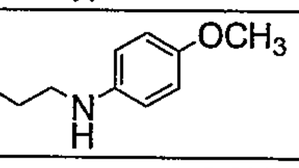
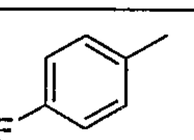
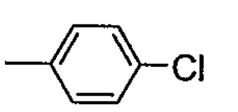
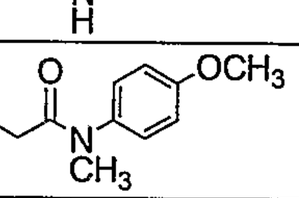
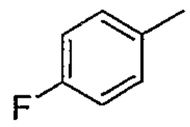
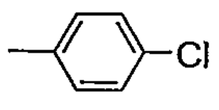
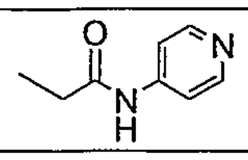
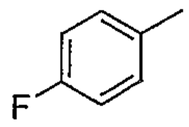
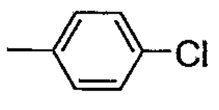
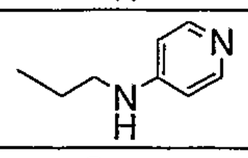
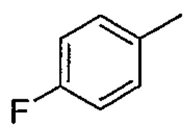
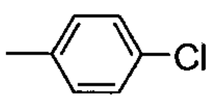
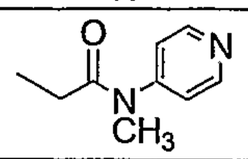
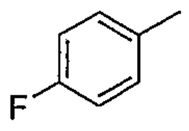
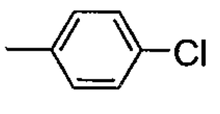
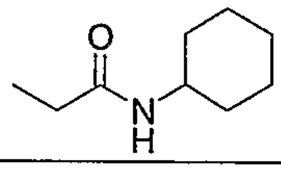
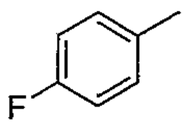
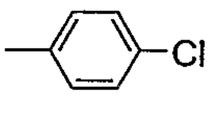
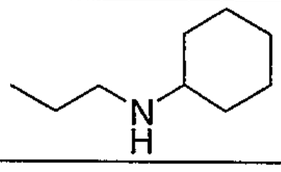
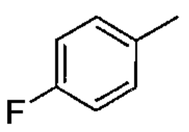
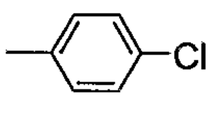
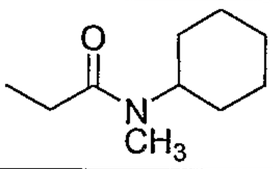
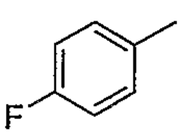
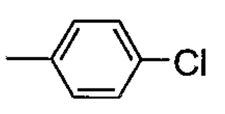
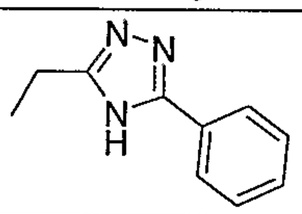
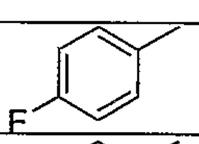
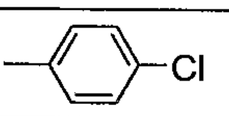
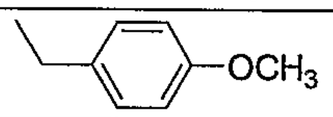
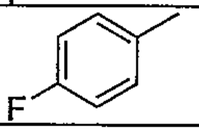
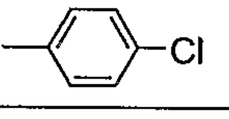
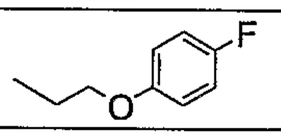
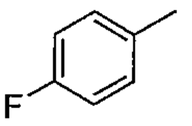
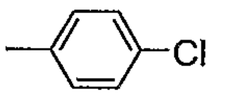
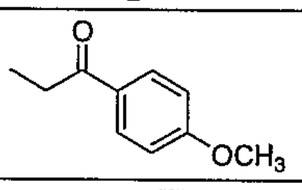
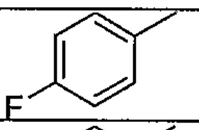
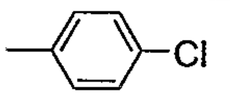
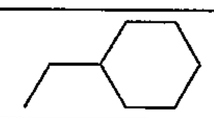
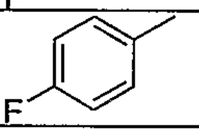
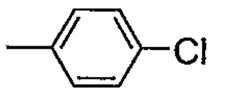
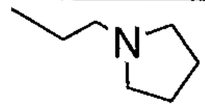
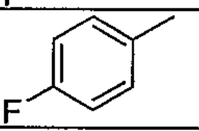
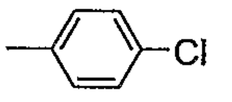
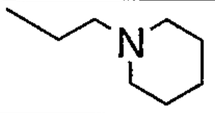
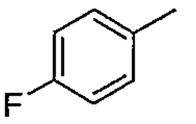
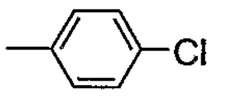
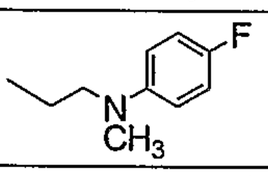
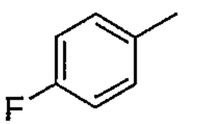
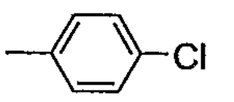
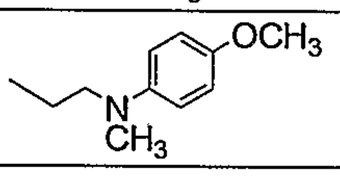
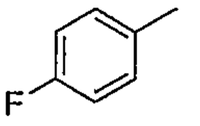
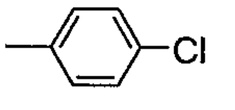
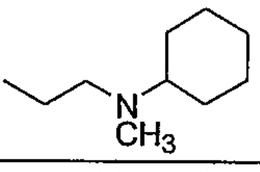
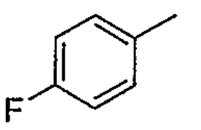
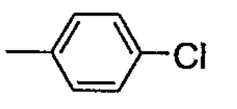
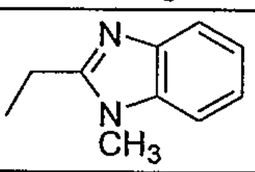
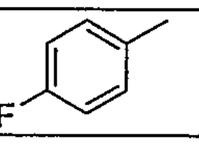
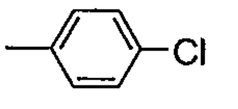
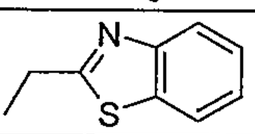
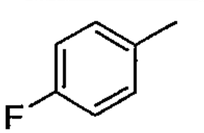
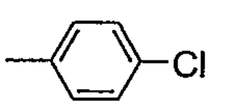
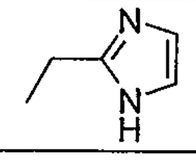
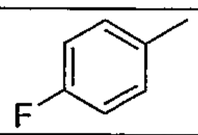
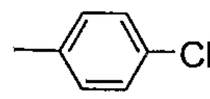
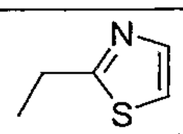
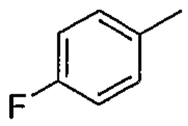
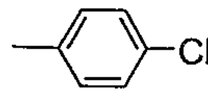
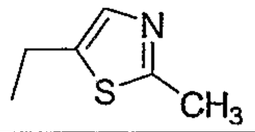
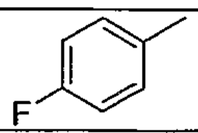
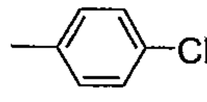
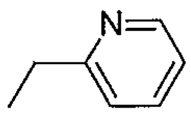
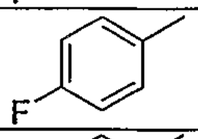
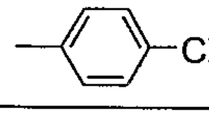
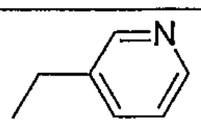
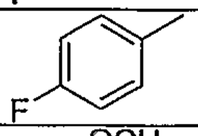
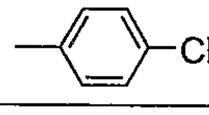
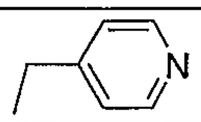
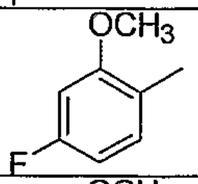
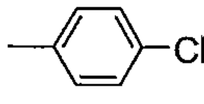
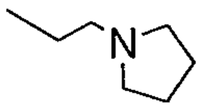
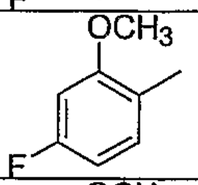
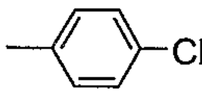
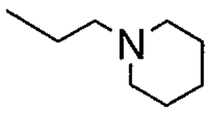
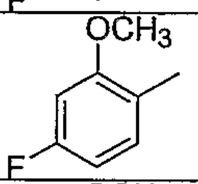
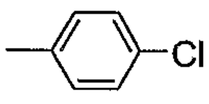
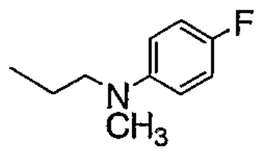
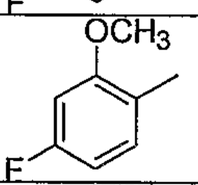
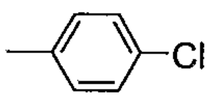
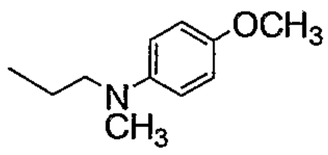
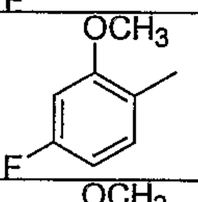
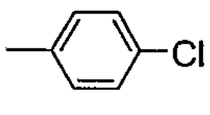
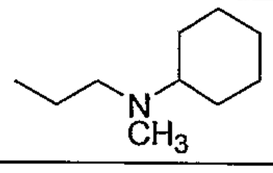
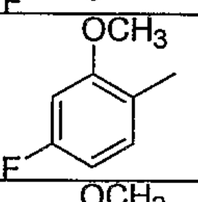
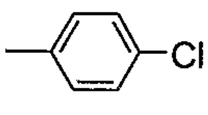
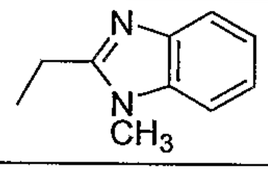
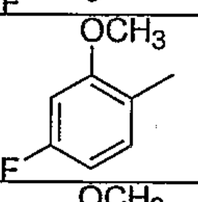
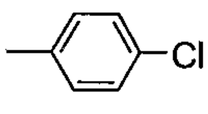
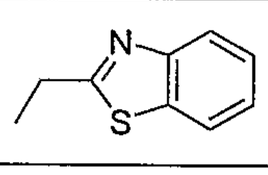
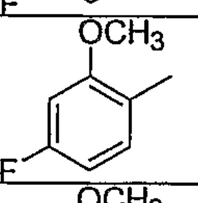
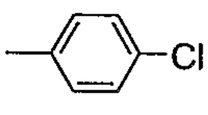
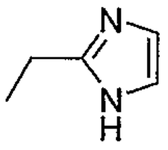
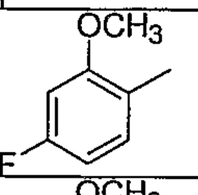
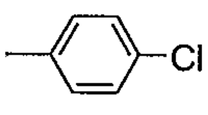
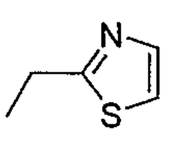
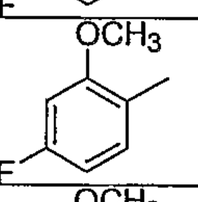
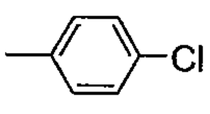
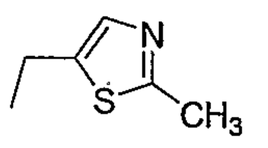
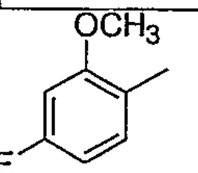
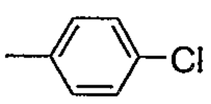
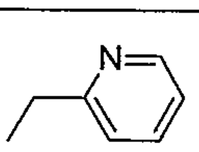
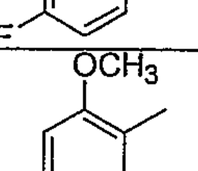
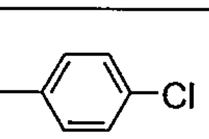
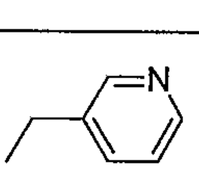
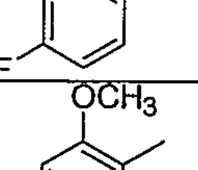
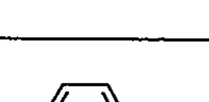
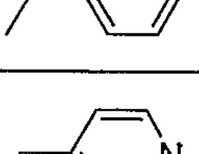
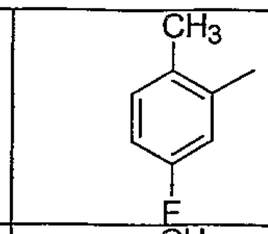
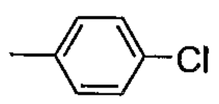
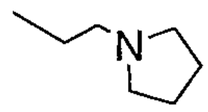
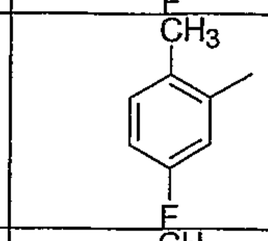
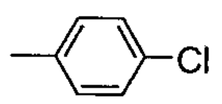
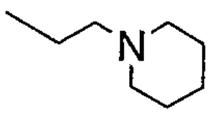
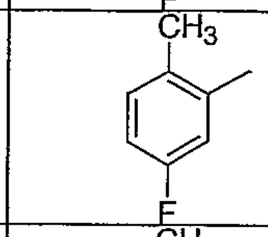
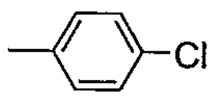
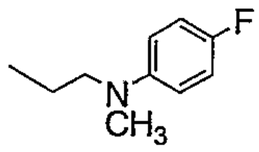
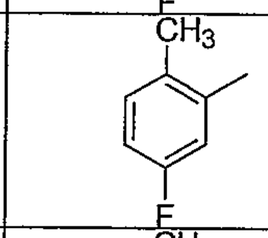
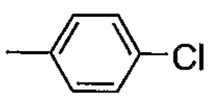
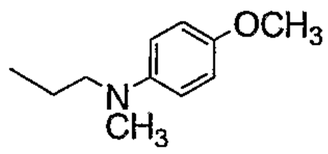
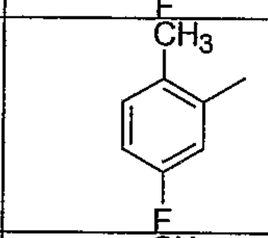
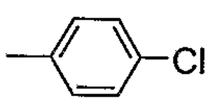
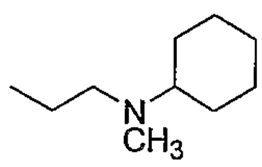
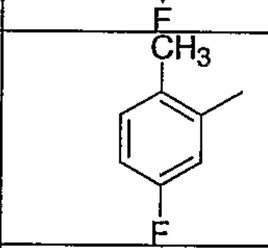
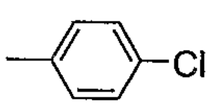
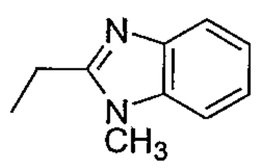
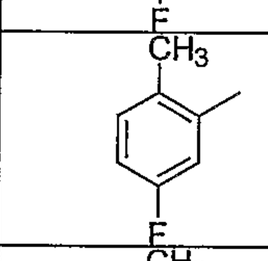
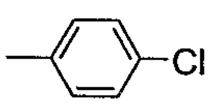
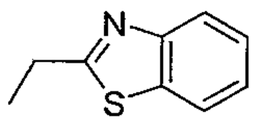
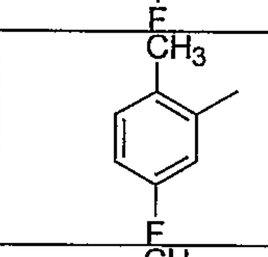
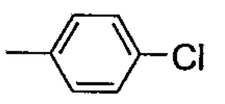
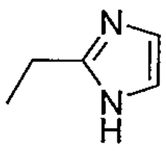
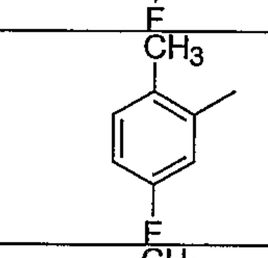
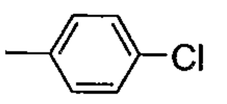
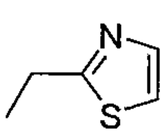
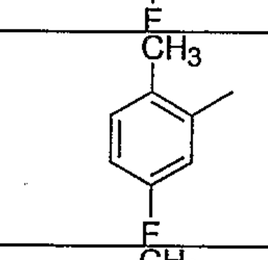
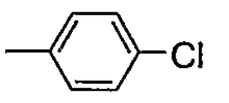
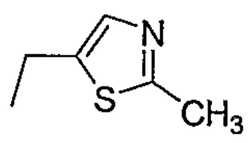
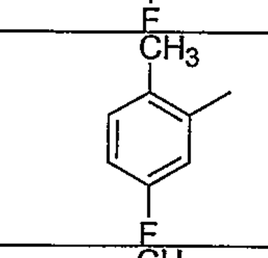
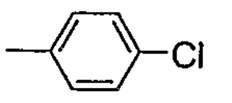
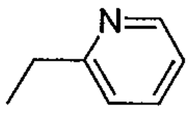
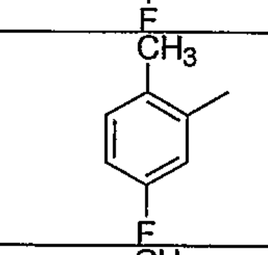
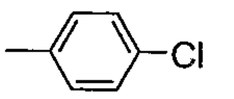
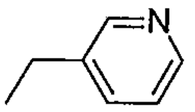
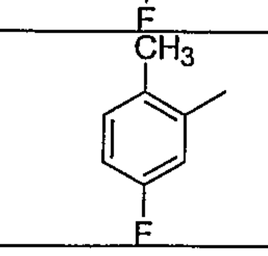
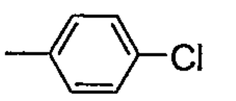
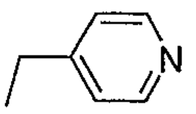
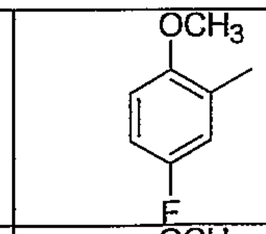
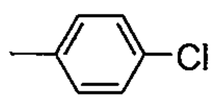
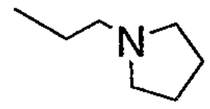
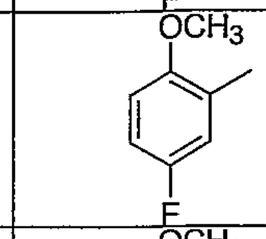
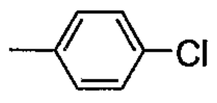
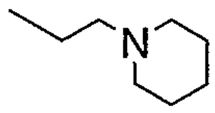
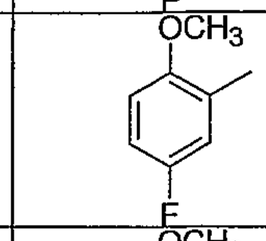
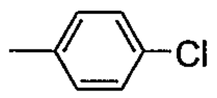
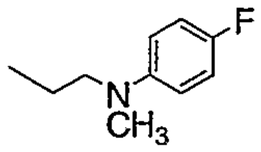
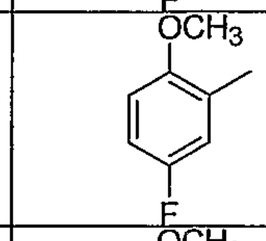
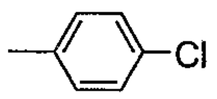
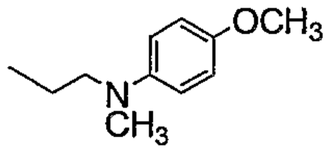
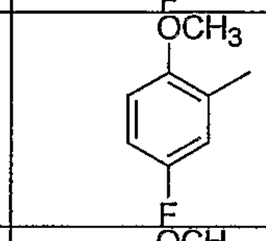
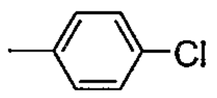
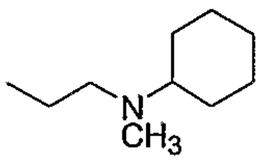
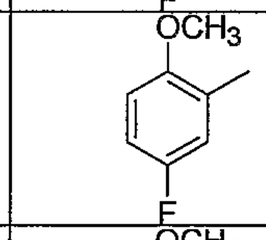
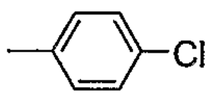
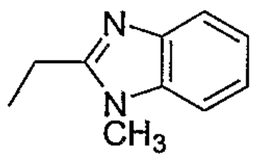
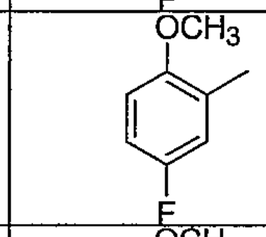
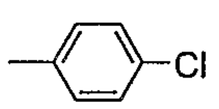
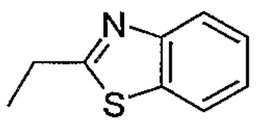
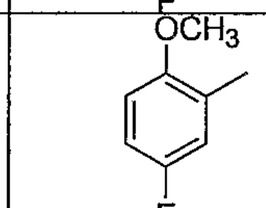
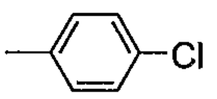
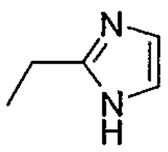
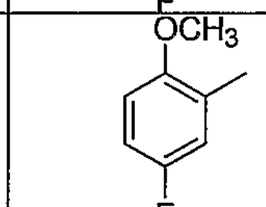
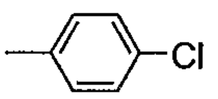
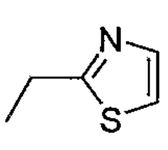
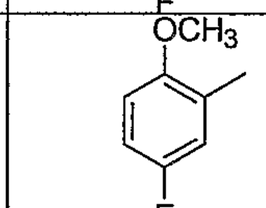
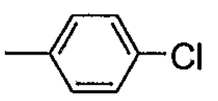
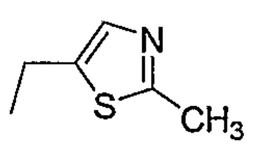
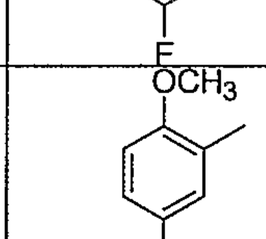
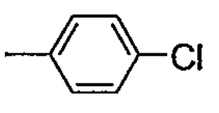
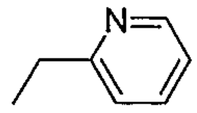
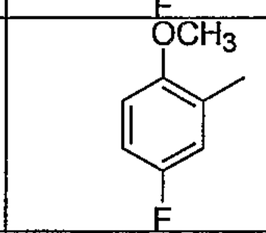
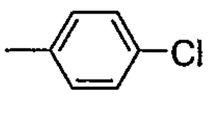
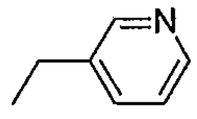
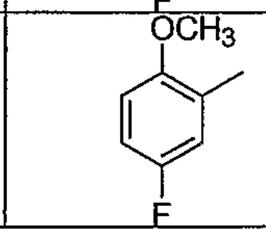
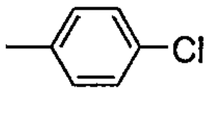
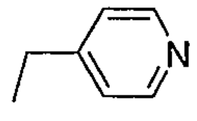
A266			

A267			
A268			
A269			
A270			
A271			
A272			
A273			
A274			
A275			
A276			
A277			
A278			
A279			
A280			
A281			
A282			
A283			
A284			

A285			
A286			
A287			
A288			
A289			
A290			
A291			
A292			
A293			
A294			
A295			
A296			
A297			
A298			
A299			
A300			
A301			
A302			
A303			

A304			
A305			
A306			
A307			
A308			
A309			
A310			
A311			
A312			
A313			
A314			
A315			
A316			
A317			
A318			
A319			
A320			
A321			

A322			
A323			
A324			
A325			
A326			
A327			
A328			
A329			
A330			
A331			
A332			
A333			
A334			

A335			
A336			
A337			
A338			
A339			
A340			
A341			
A342			
A343			
A344			
A345			
A346			
A347			

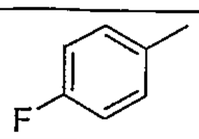
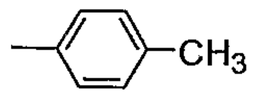
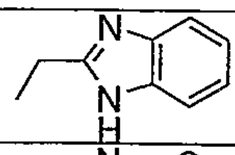
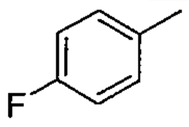
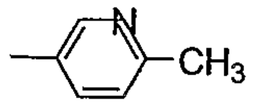
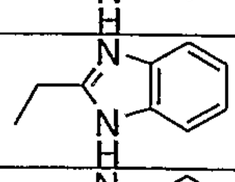
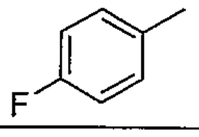
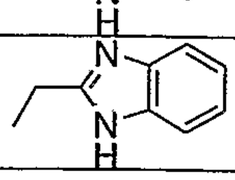
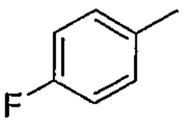
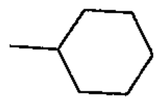
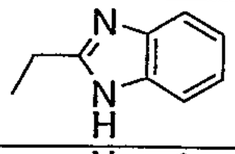
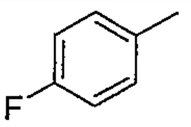
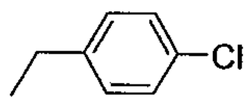
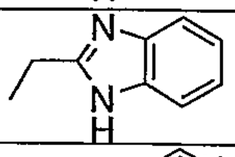
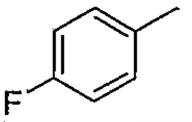
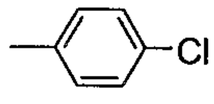
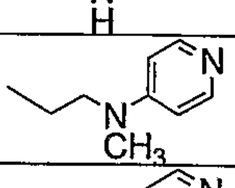
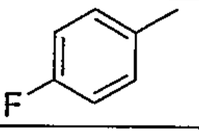
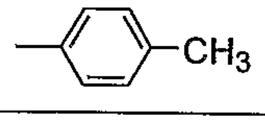
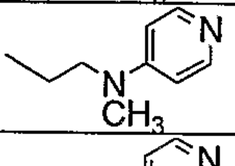
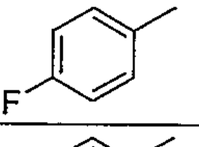
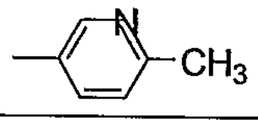
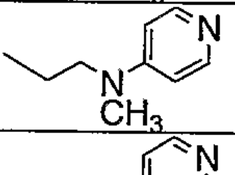
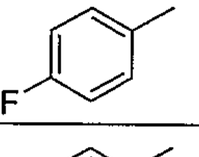
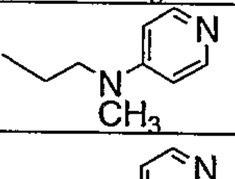
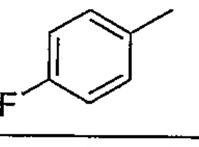
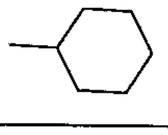
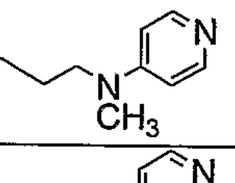
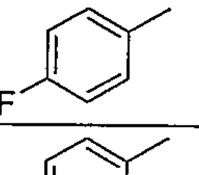
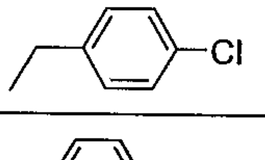
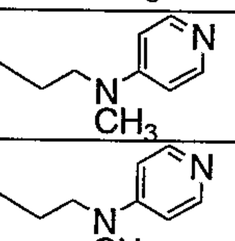
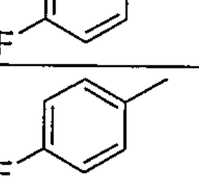
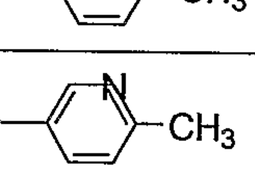
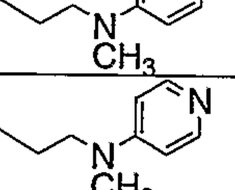
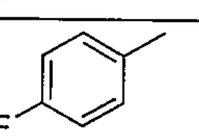
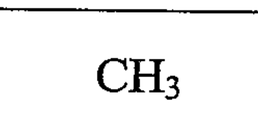
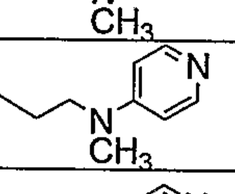
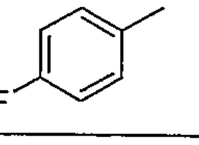
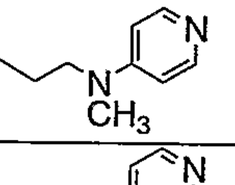
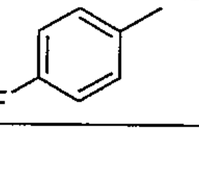
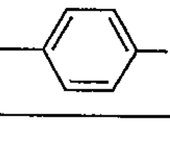
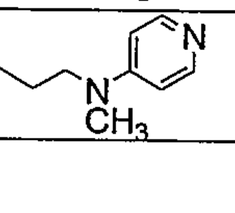
A348			
A349			
A350		CH_3	
A351			
A352			
A353			
A354			
A355			
A356		CH_3	
A357			
A358			
A359			
A360			
A361		CH_3	
A362			
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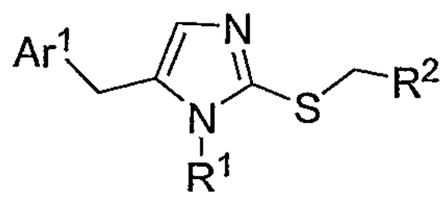
TABLE A1D



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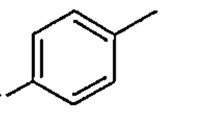
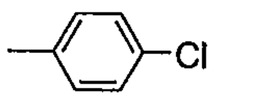
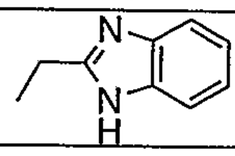
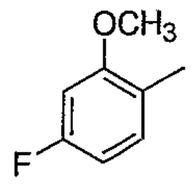
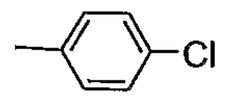
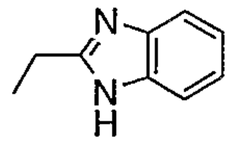
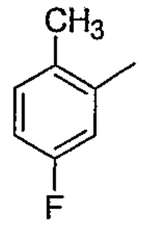
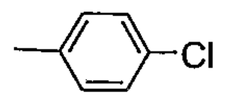
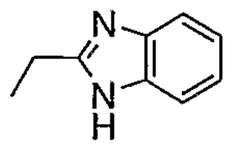
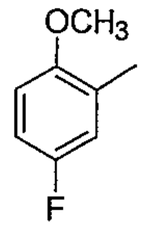
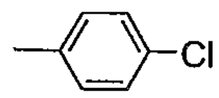
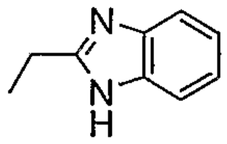
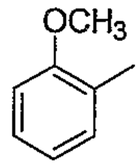
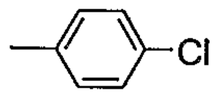
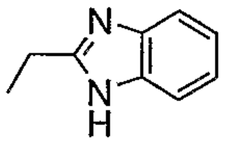
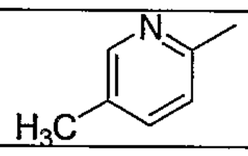
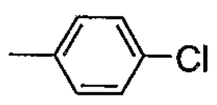
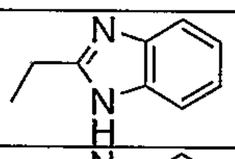
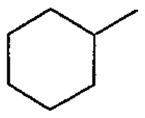
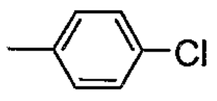
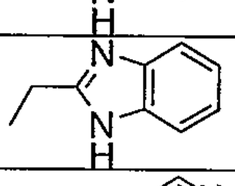
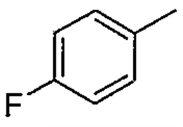
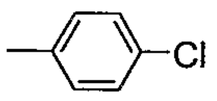
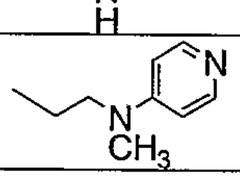
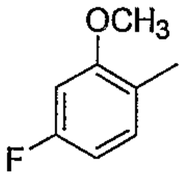
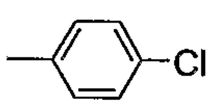
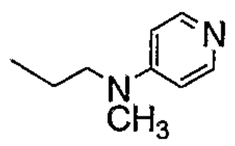
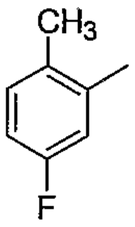
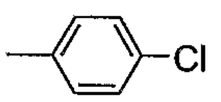
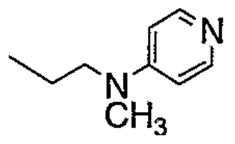
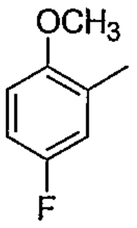
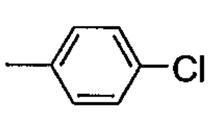
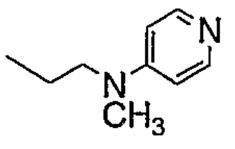
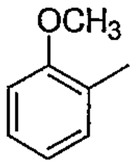
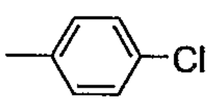
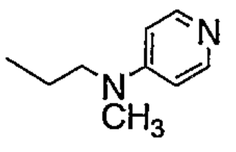
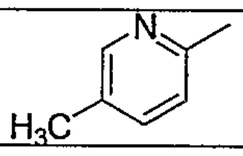
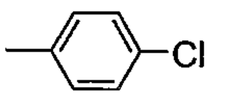
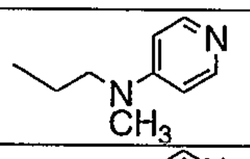
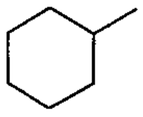
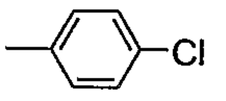
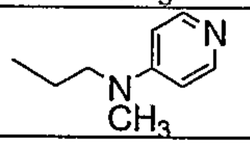
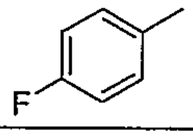
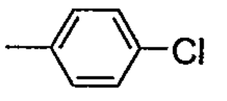
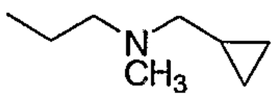
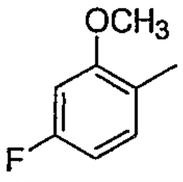
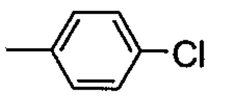
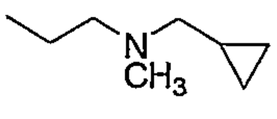
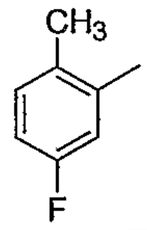
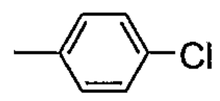
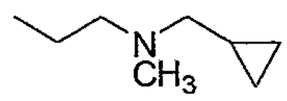
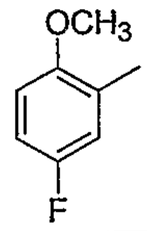
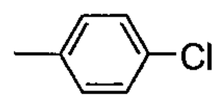
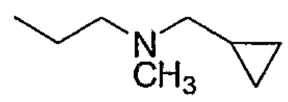
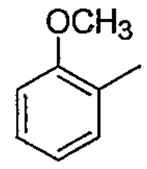
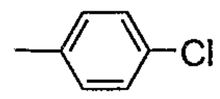
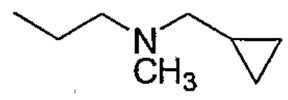
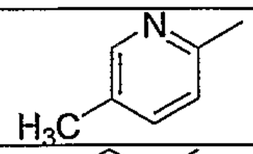
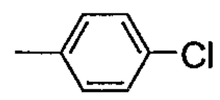
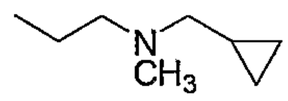
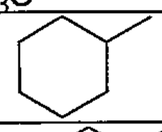
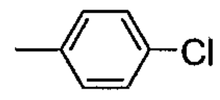
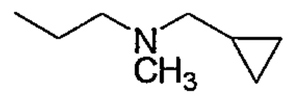
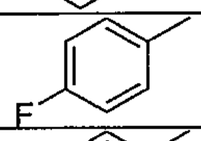
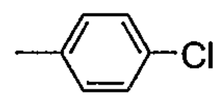
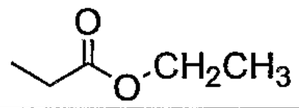
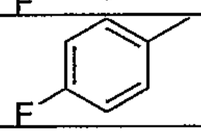
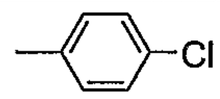
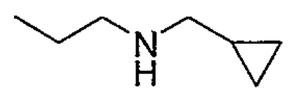
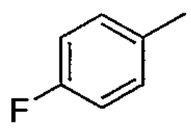
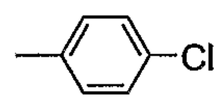
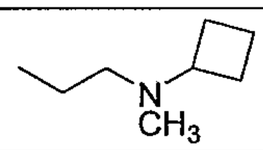
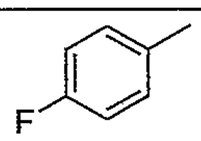
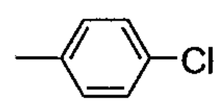
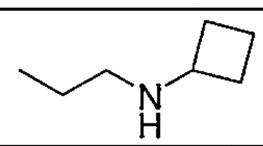
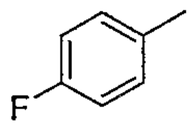
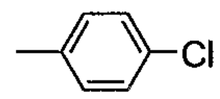
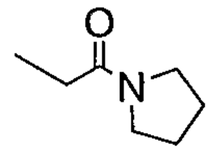
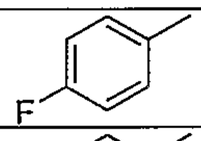
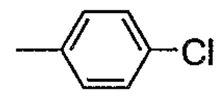
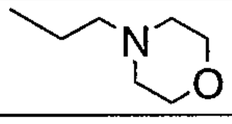
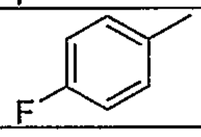
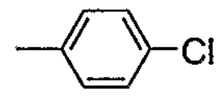
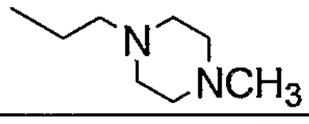
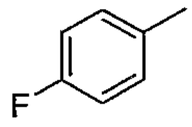
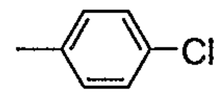
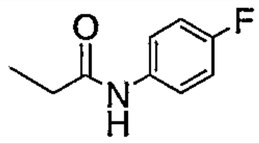
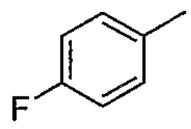
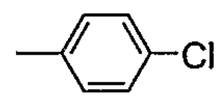
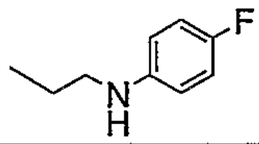
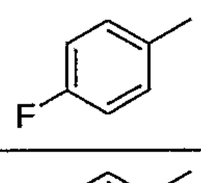
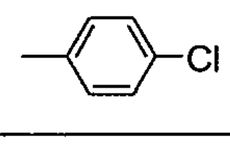
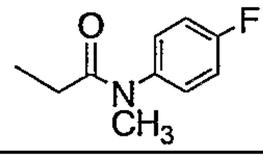
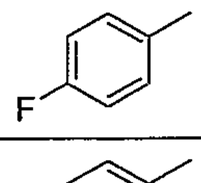
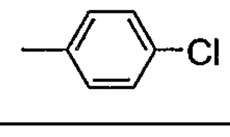
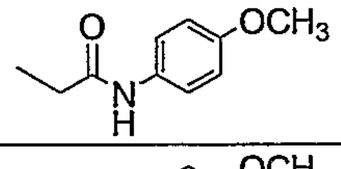
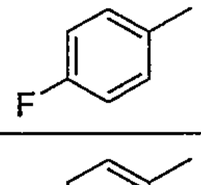
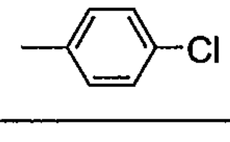
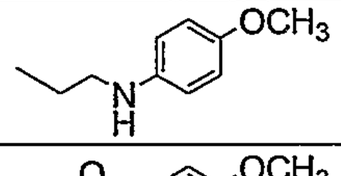
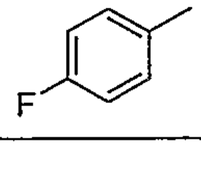
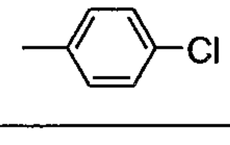
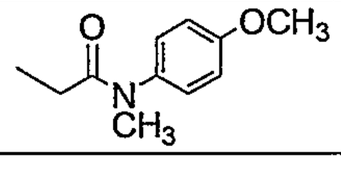
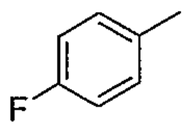
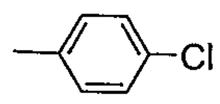
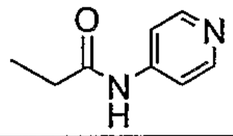
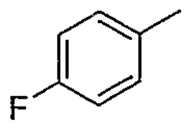
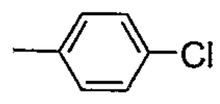
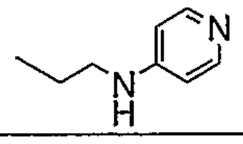
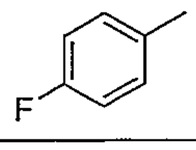
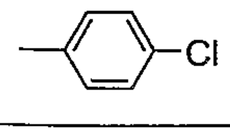
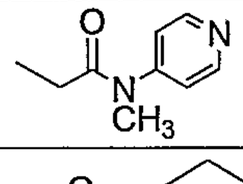
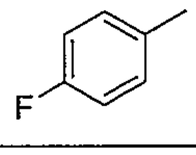
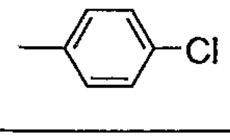
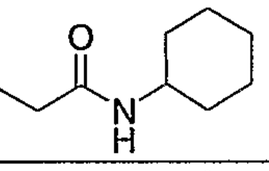
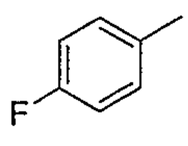
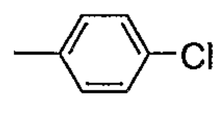
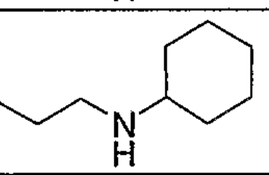
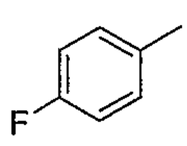
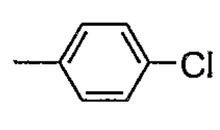
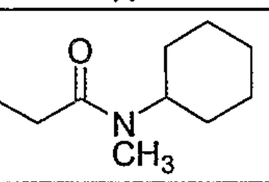
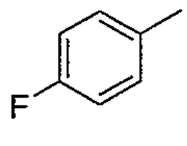
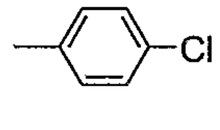
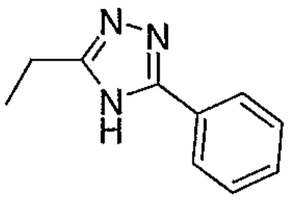
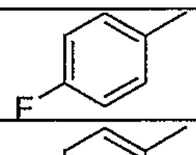
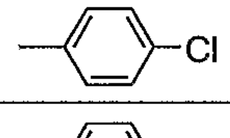
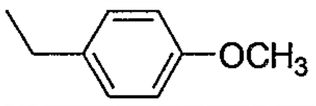
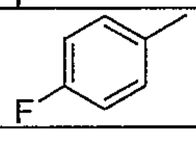
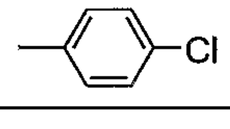
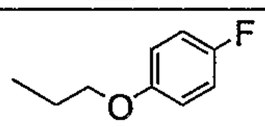
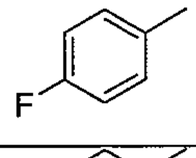
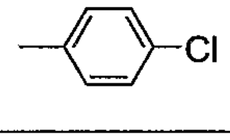
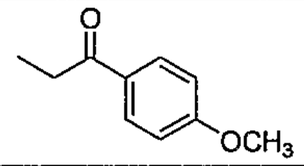
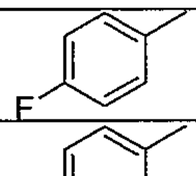
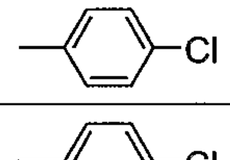
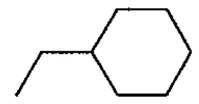
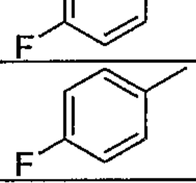
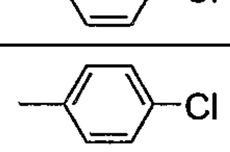
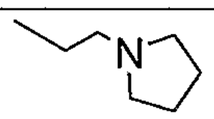
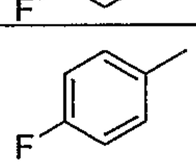
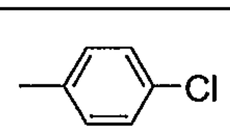
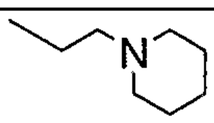
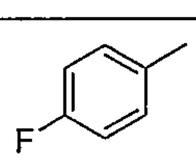
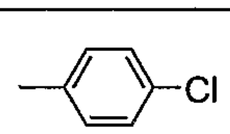
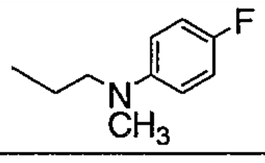
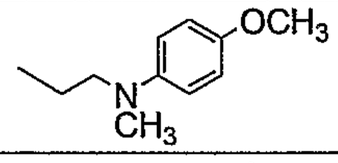
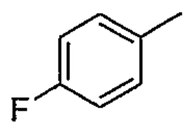
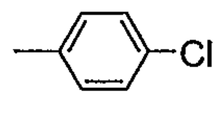
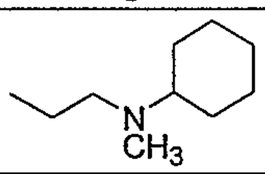
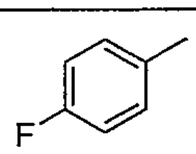
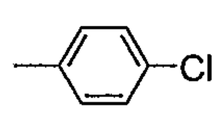
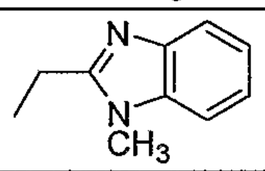
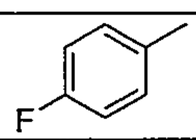
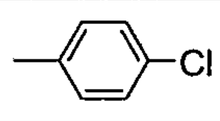
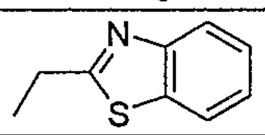
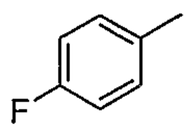
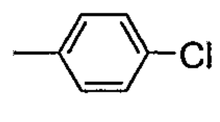
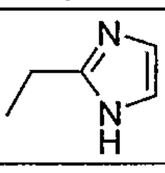
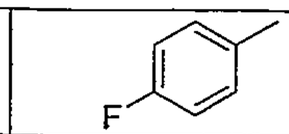
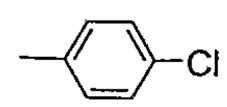
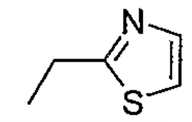
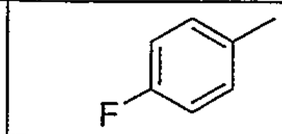
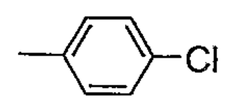
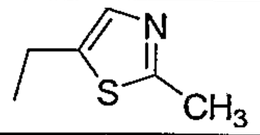
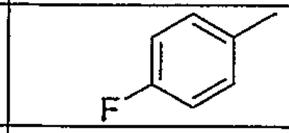
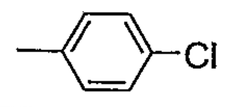
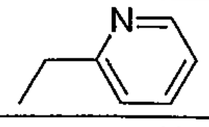
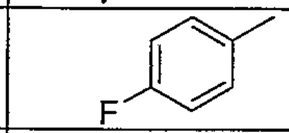
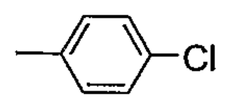
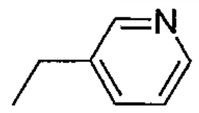
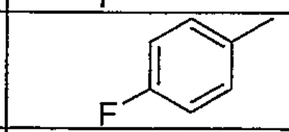
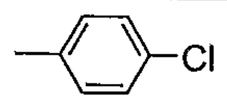
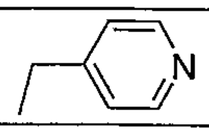
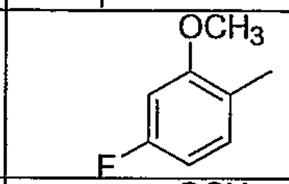
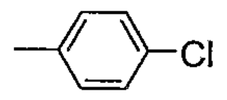
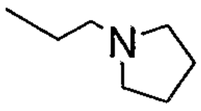
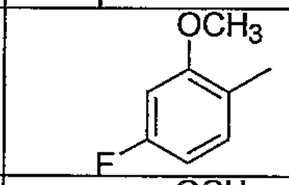
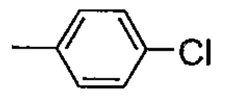
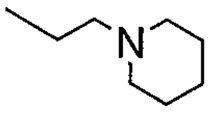
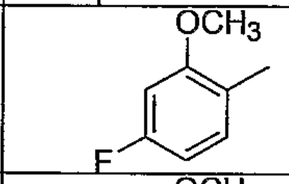
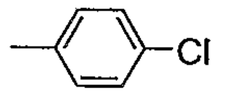
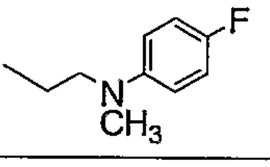
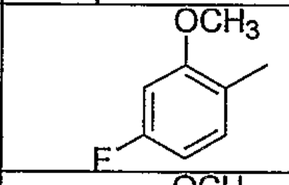
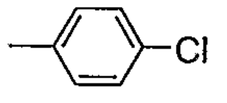
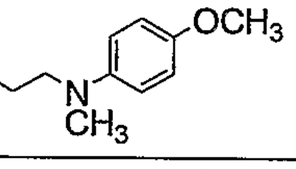
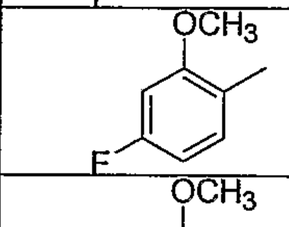
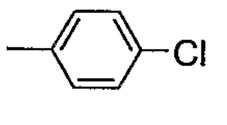
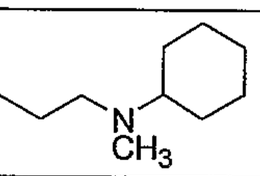
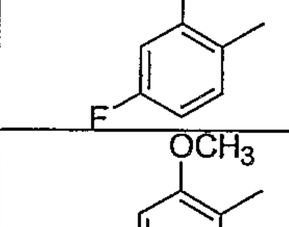
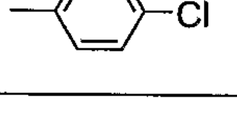
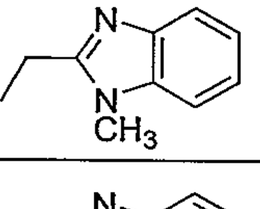
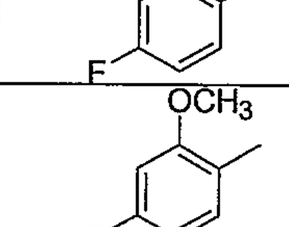
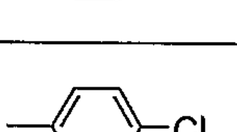
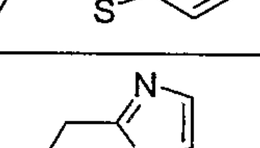
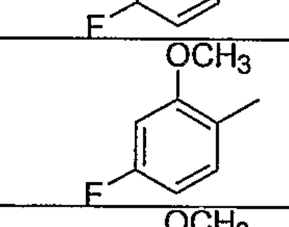
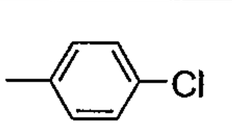
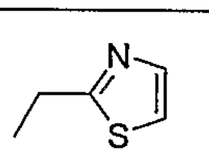
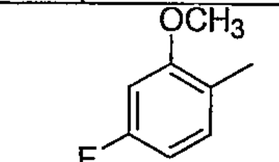
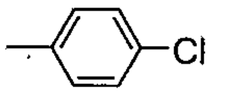
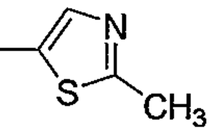
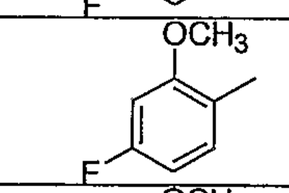
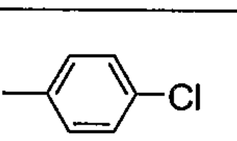
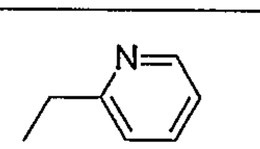
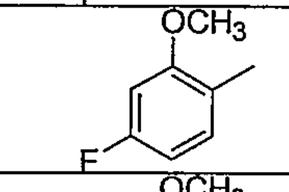
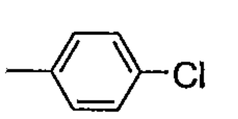
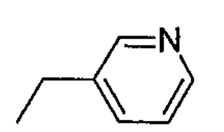
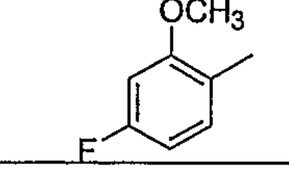
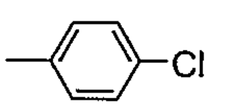
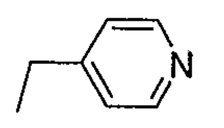
A364			

A365			
A366			
A367			
A368			
A369			
A370			
A371			
A372			
A373			
A374			
A375			
A376			
A377			
A378			
A379			

A380			
A381			
A382			
A383			
A384			
A385			
A386			
A387			
A388			
A389			
A390			
A391			
A392			
A393			
A394			
A395			
A396			
A397			

A398			
A399			
A400			
A401			
A402			
A403			
A404			
A405			
A406			
A407			
A408			
A409			
A410			
A411			
A412			
A413			
A414			
A415			
A416			

A417			
A418			
A419			
A420			
A421			
A422			
A423			
A424			
A425			
A426			
A427			
A428			
A429			
A430			
A431			
A432			
A433			
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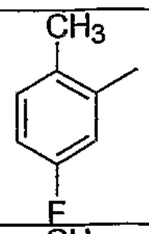
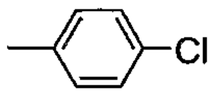
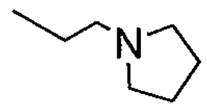
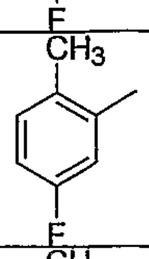
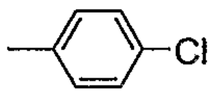
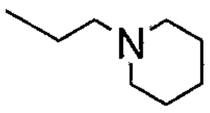
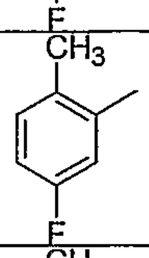
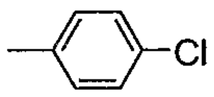
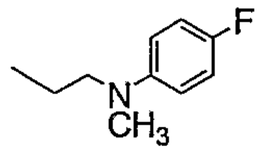
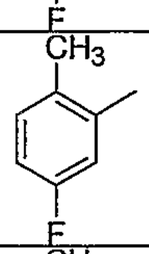
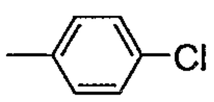
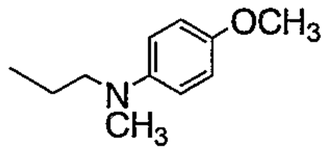
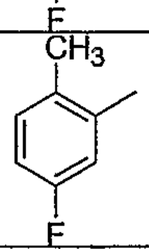
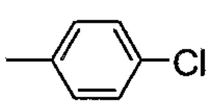
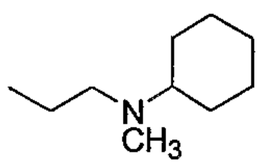
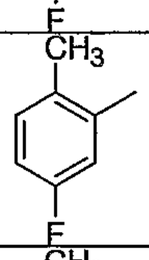
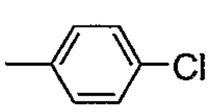
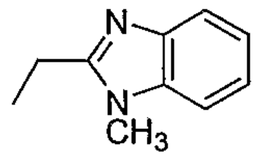
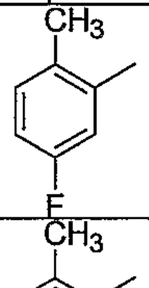
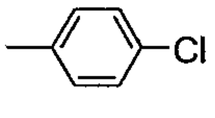
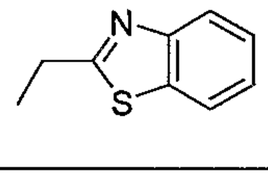
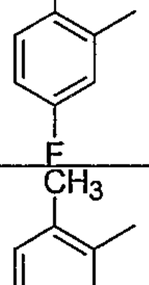
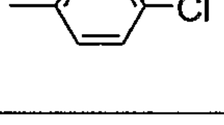
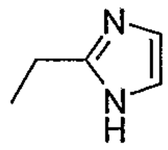
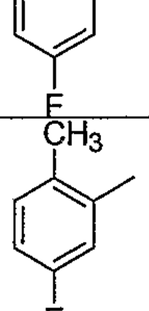
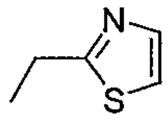
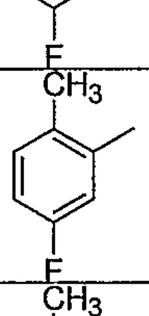
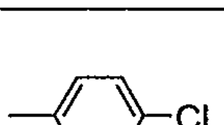
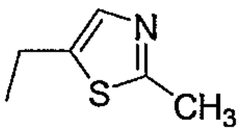
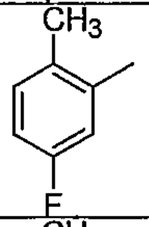
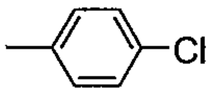
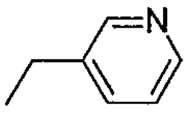
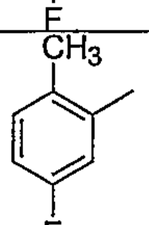
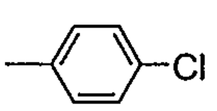
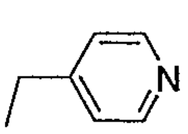
A435			
A436			
A437			
A438			
A439			
A440			
A441			
A442			
A443			
A444			
A445			
A446			
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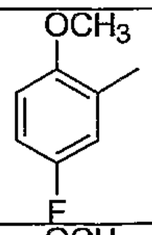
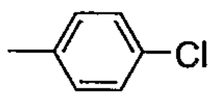
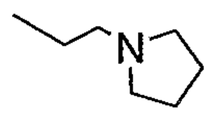
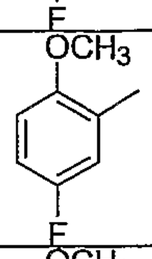
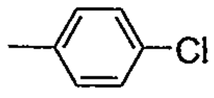
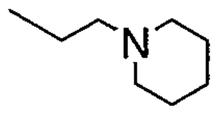
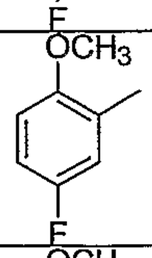
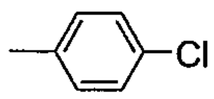
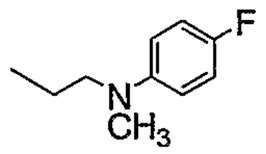
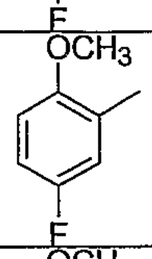
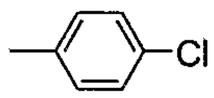
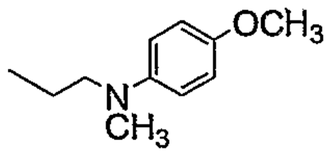
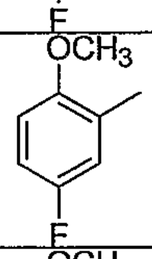
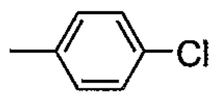
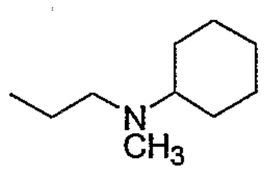
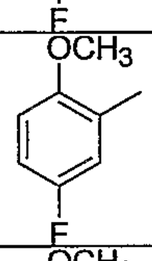
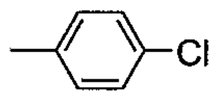
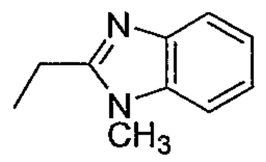
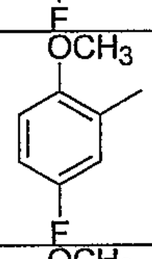
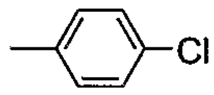
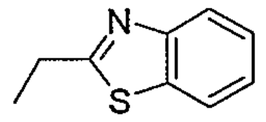
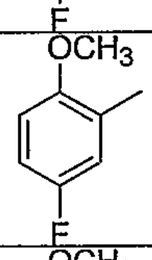
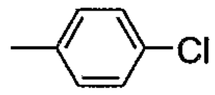
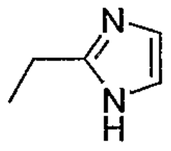
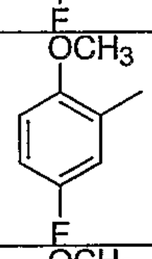
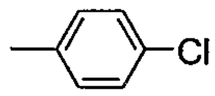
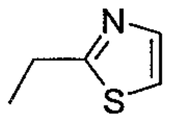
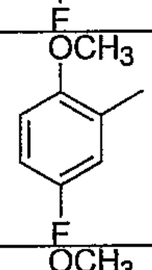
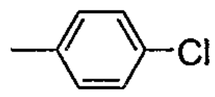
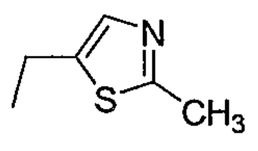
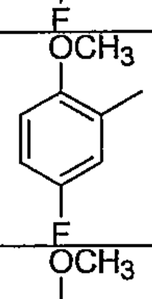
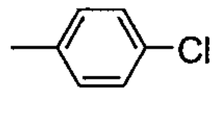
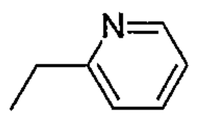
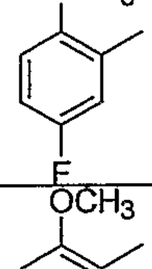
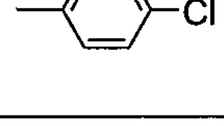
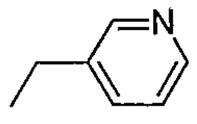
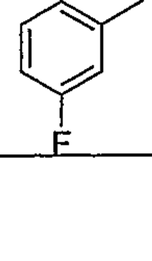
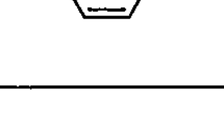
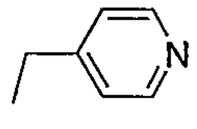
A448			
A449			
A450			
A451			
A452			
A453			
A454			
A455			
A456			
A457			
A458			
A459			
A460			

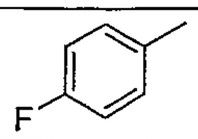
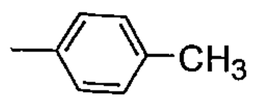
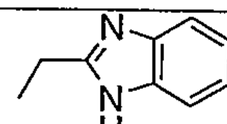
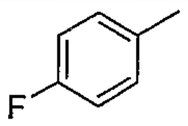
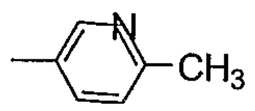
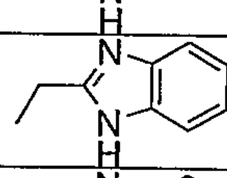
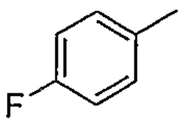
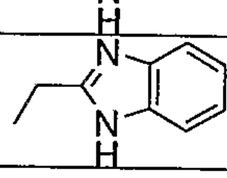
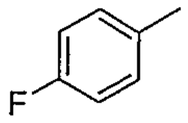
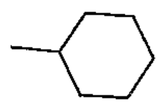
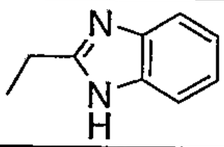
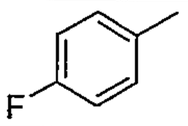
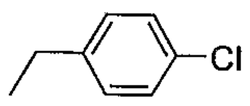
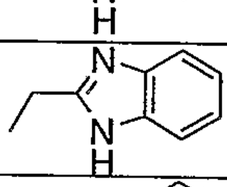
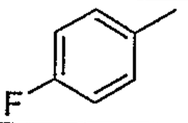
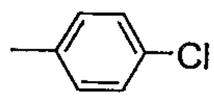
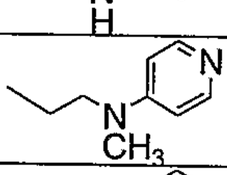
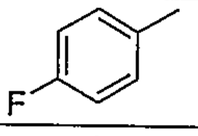
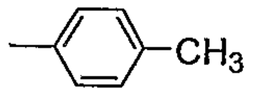
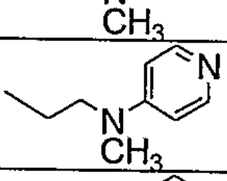
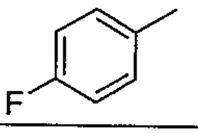
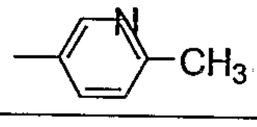
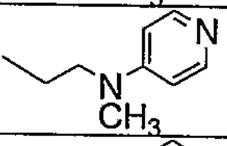
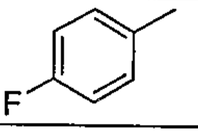
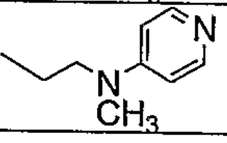
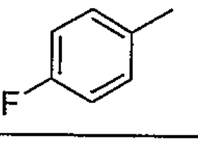
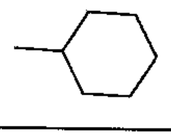
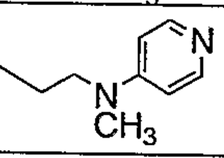
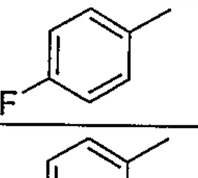
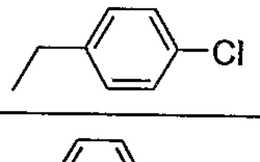
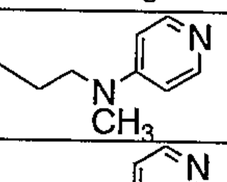
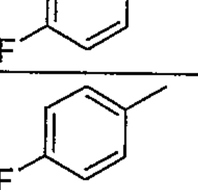
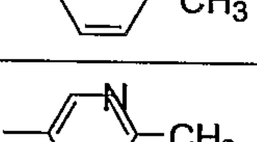
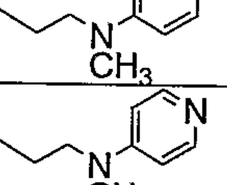
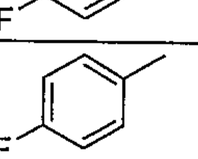
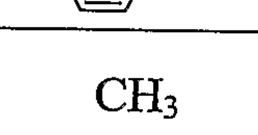
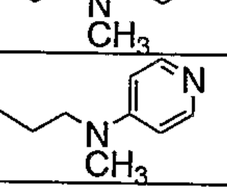
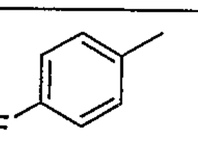
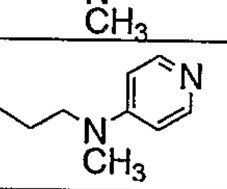
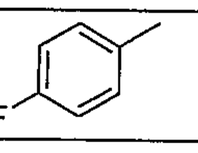
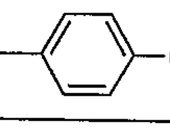
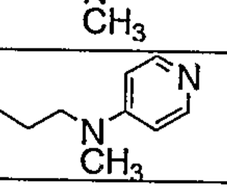
A461			
A462			
A463		CH_3	
A464			
A465			
A466			
A467			
A468			
A469		CH_3	
A470			
A471			
A472			
A473			
A474		CH_3	
A475			
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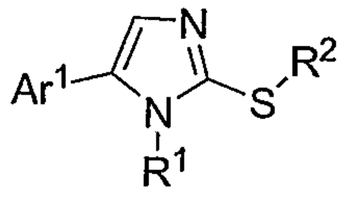
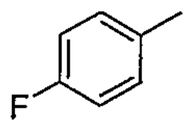
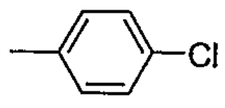
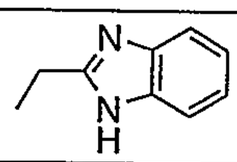
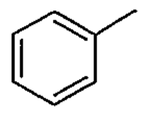
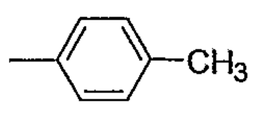
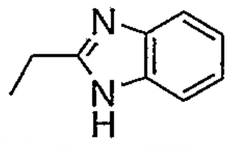
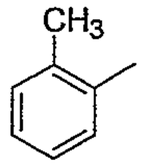
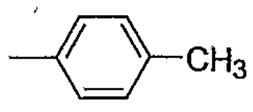
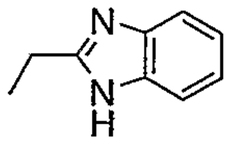
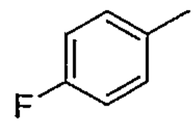
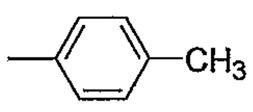
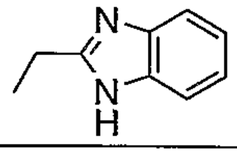
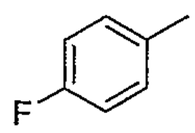
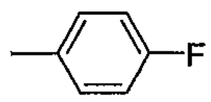
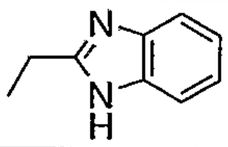
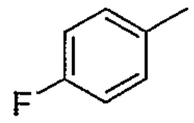
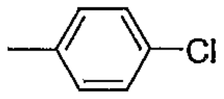
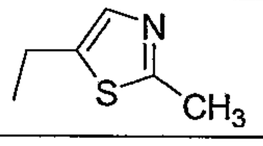
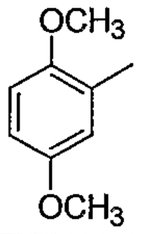
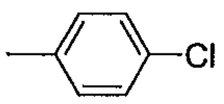
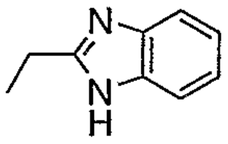
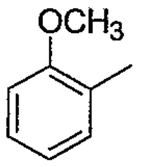
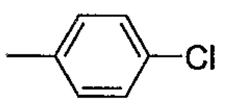
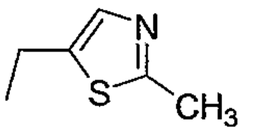
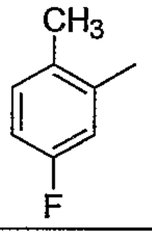
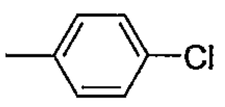
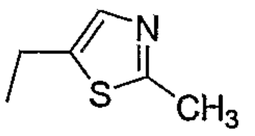
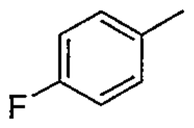
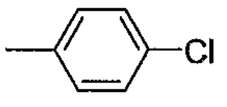
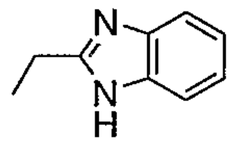
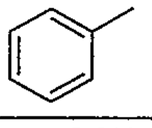
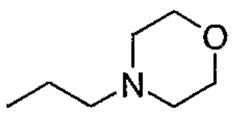
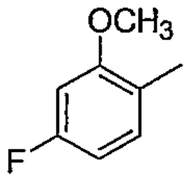
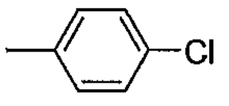
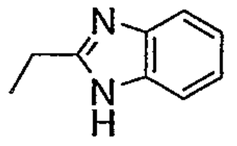
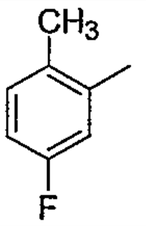
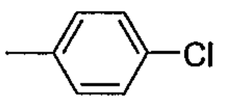
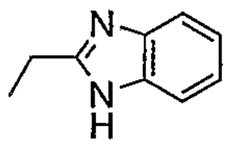
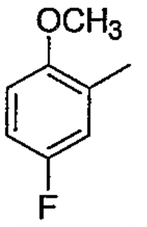
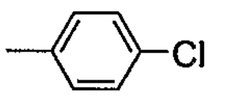
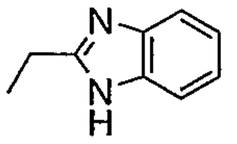
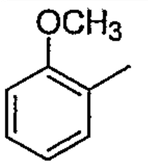
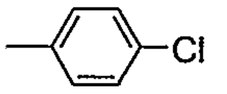
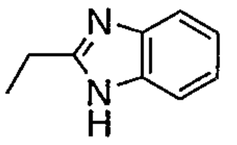
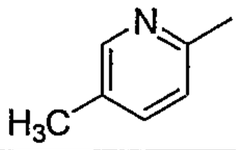
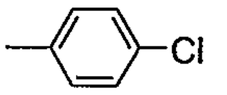
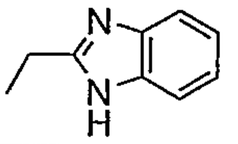
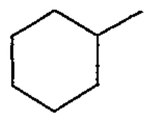
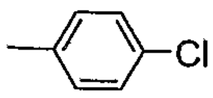
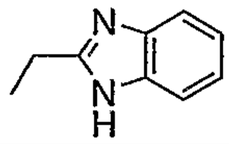
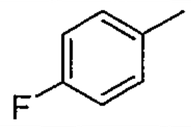
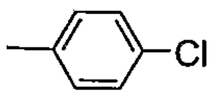
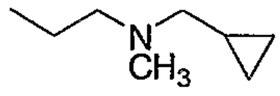
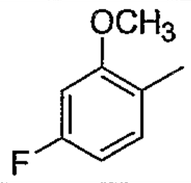
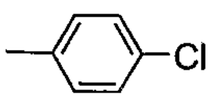
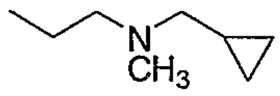
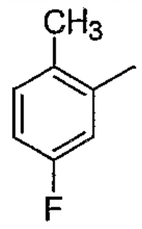
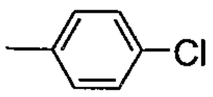
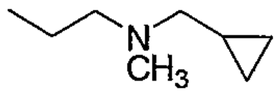
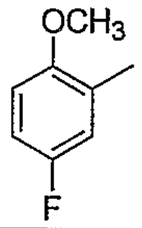
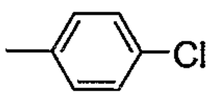
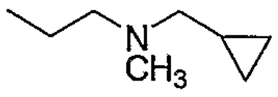
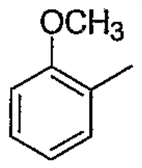
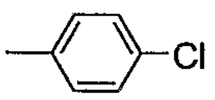
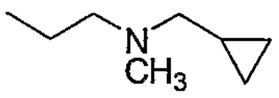
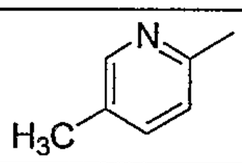
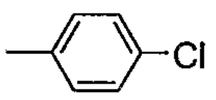
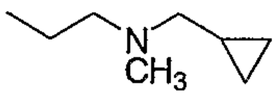
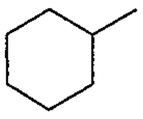
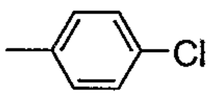
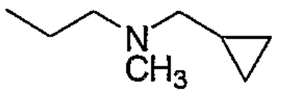
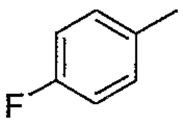
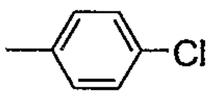
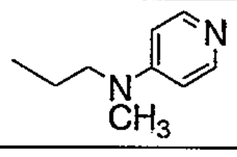
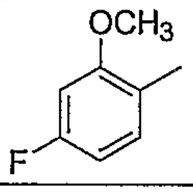
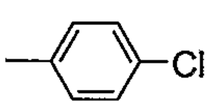
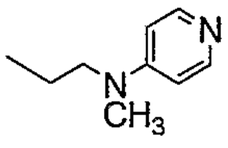
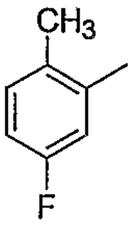
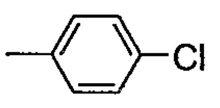
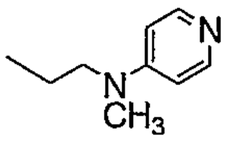
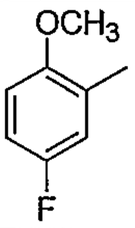
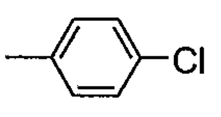
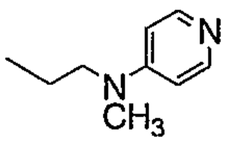
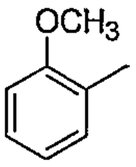
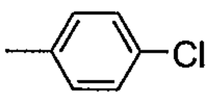
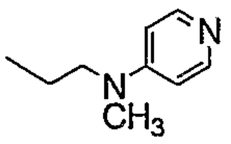
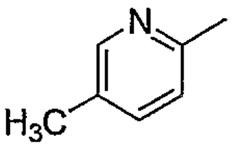
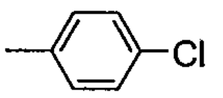
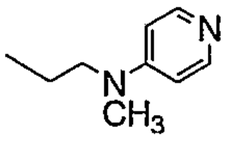
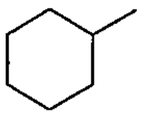
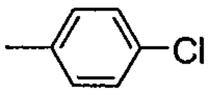
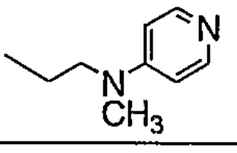
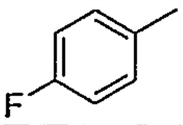
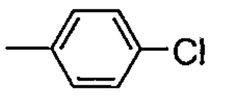
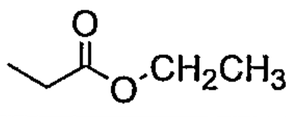
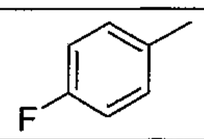
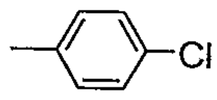
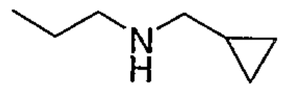
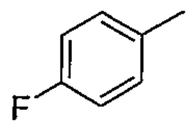
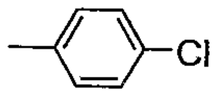
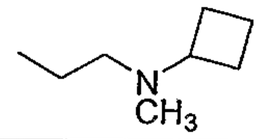
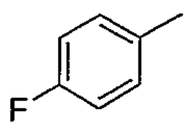
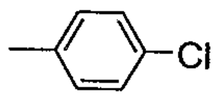
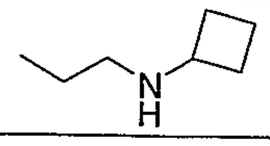
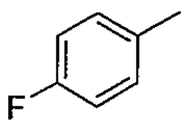
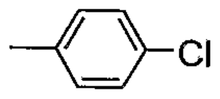
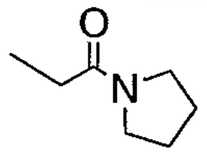
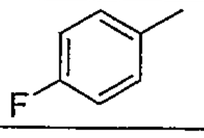
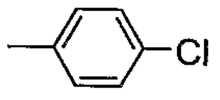
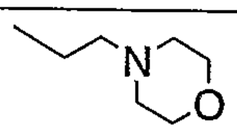
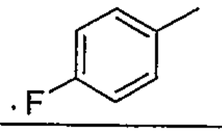
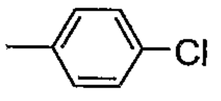
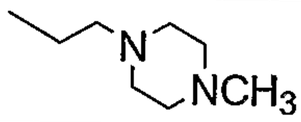
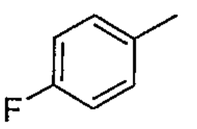
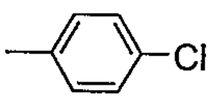
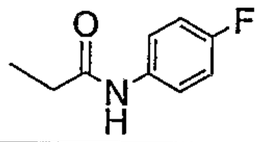
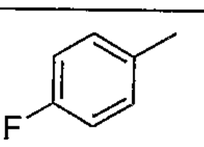
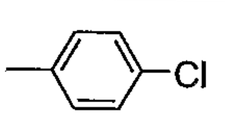
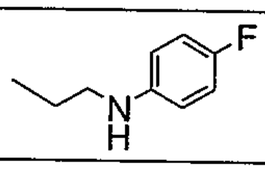
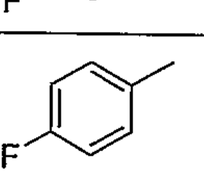
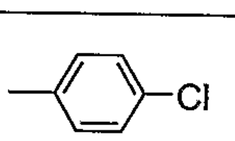
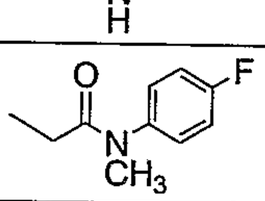
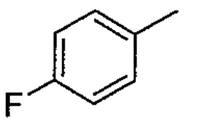
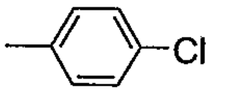
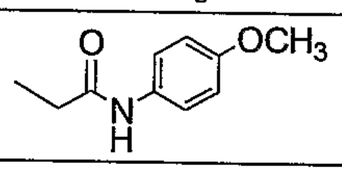
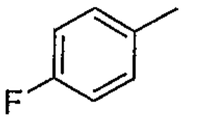
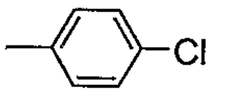
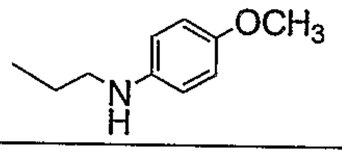
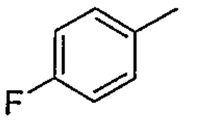
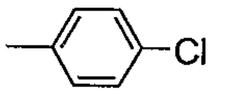
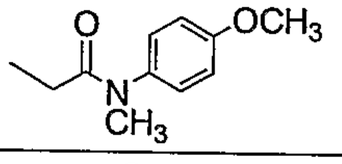
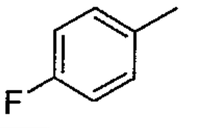
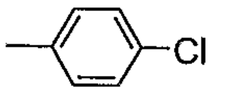
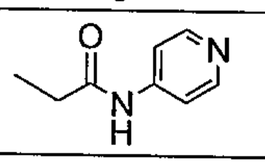
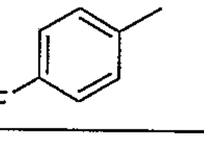
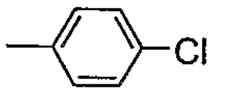
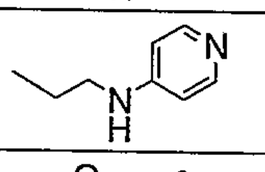
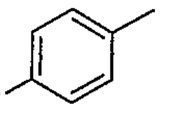
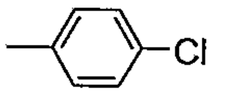
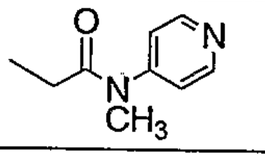
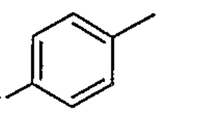
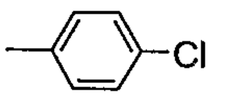
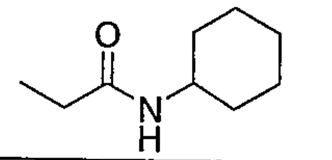
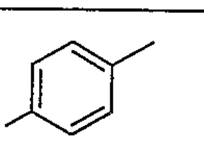
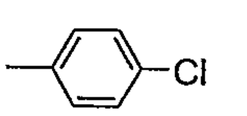
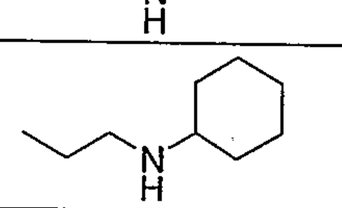
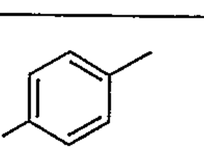
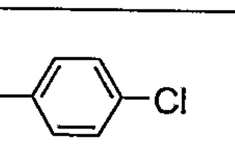
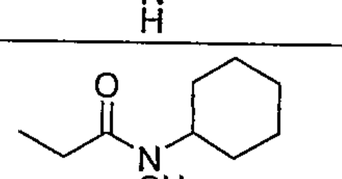
TABLE B1A

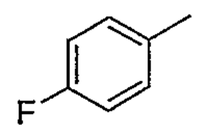
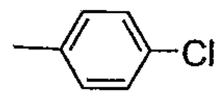
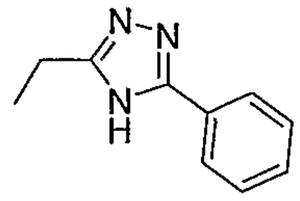
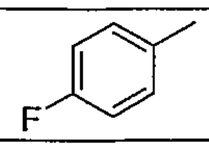
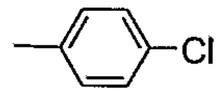
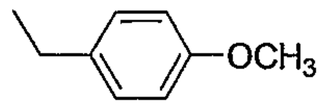
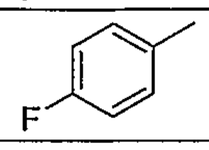
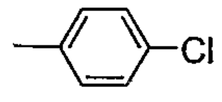
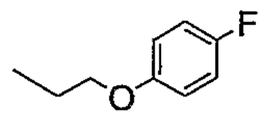
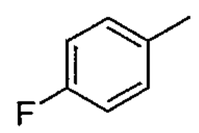
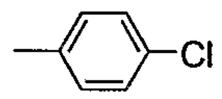
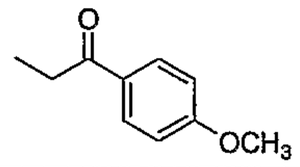
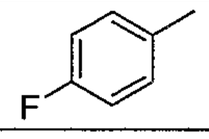
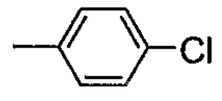
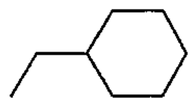
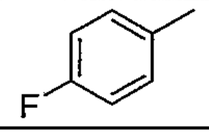
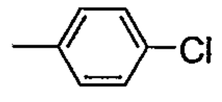
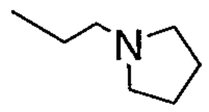
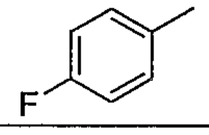
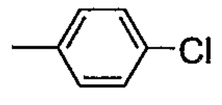
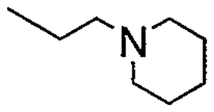
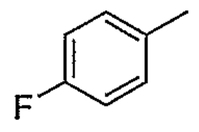
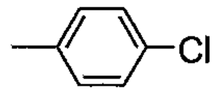
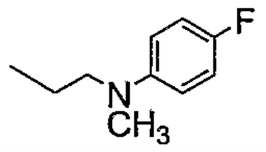
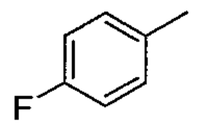
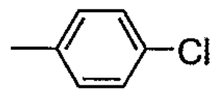
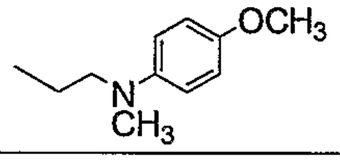
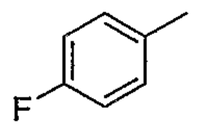
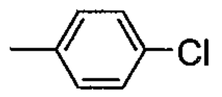
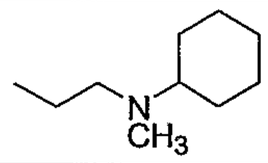
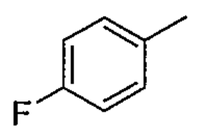
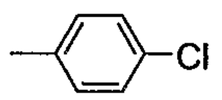
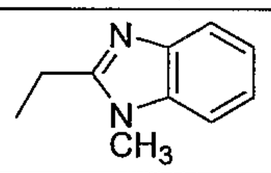
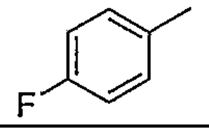
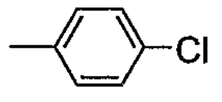
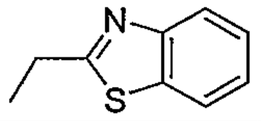
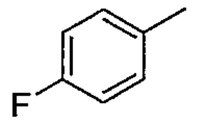
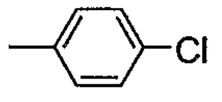
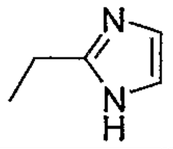
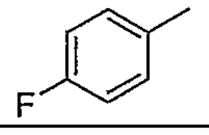
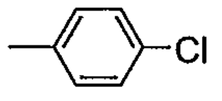
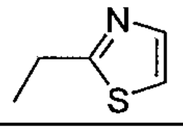
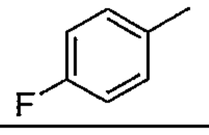
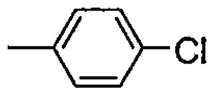
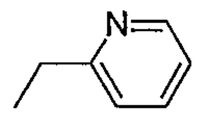
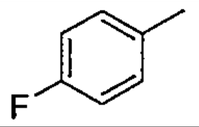
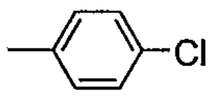
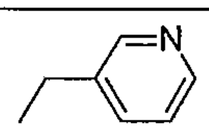
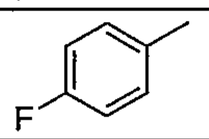
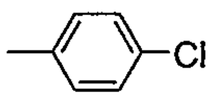
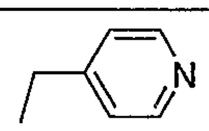
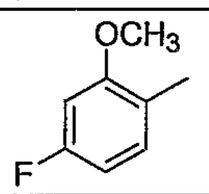
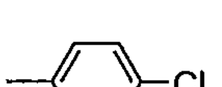
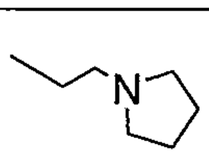


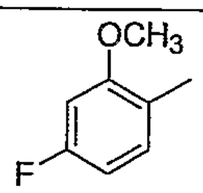
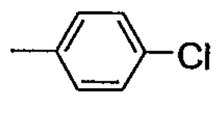
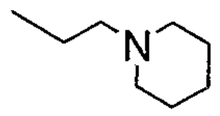
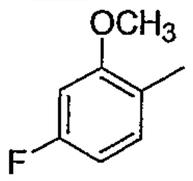
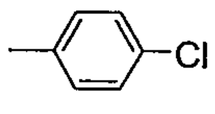
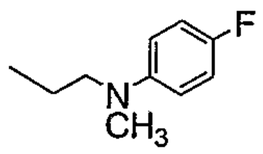
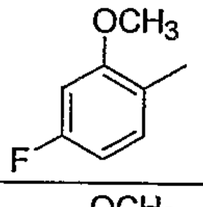
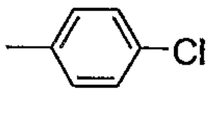
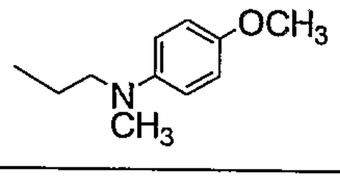
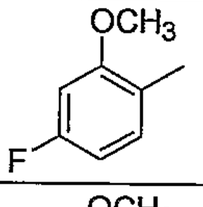
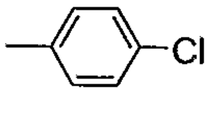
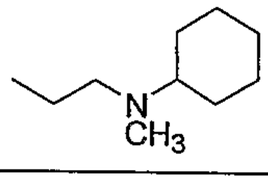
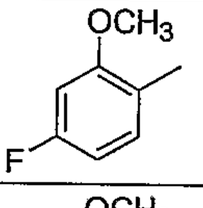
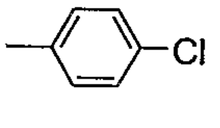
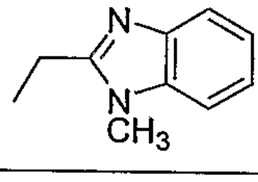
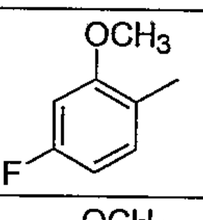
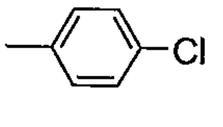
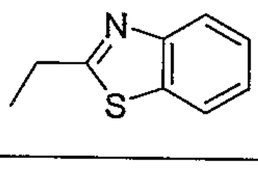
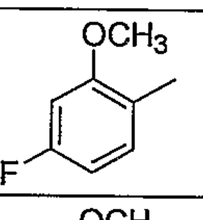
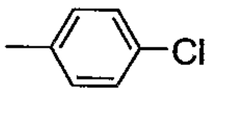
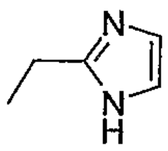
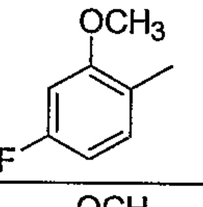
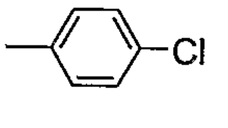
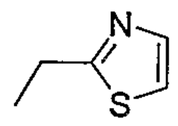
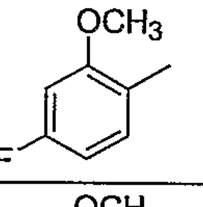
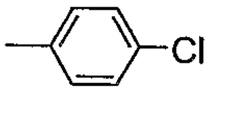
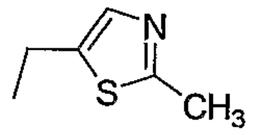
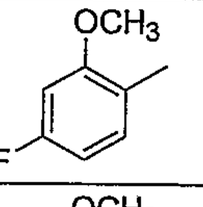
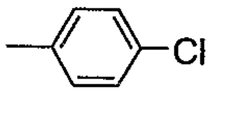
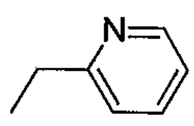
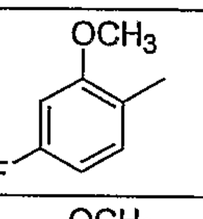
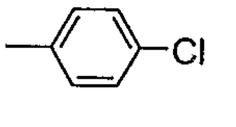
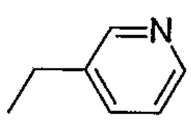
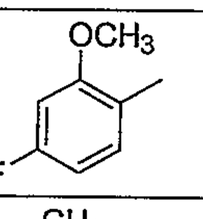
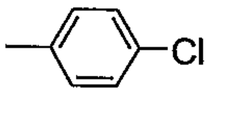
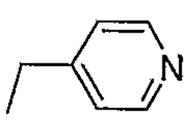
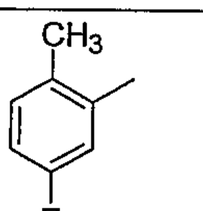
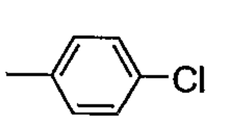
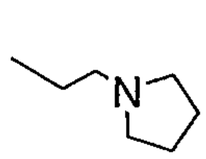
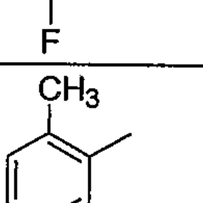
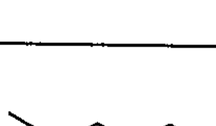
Cpd No.	Ar^1	R^1	R^2
B1			

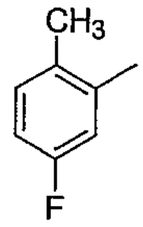
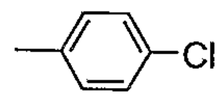
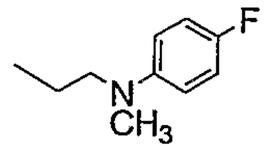
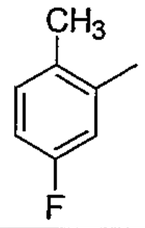
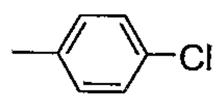
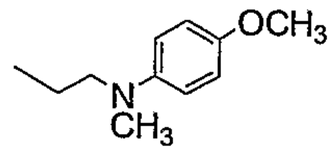
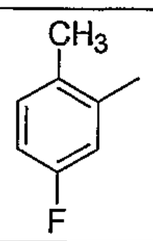
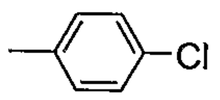
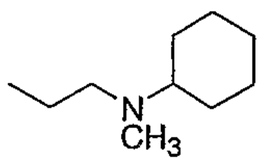
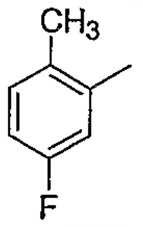
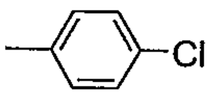
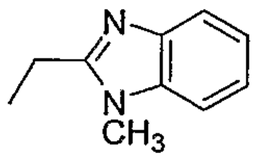
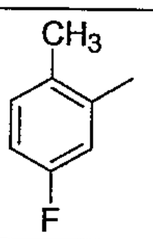
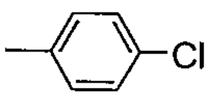
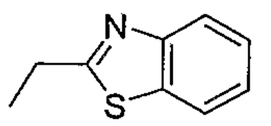
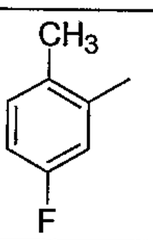
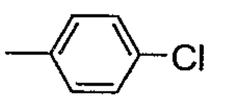
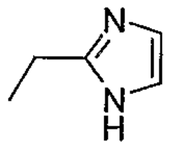
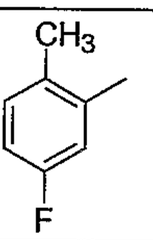
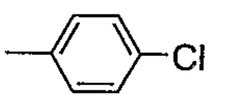
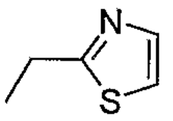
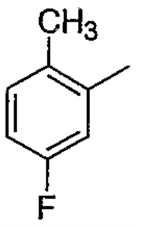
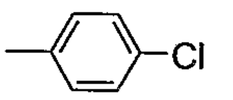
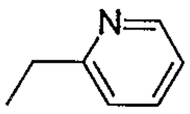
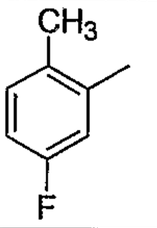
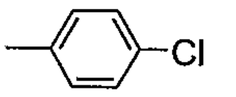
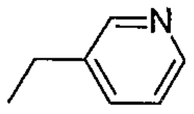
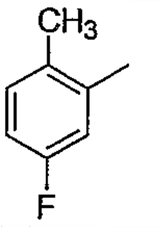
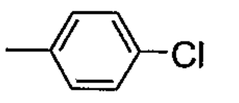
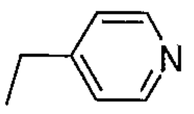
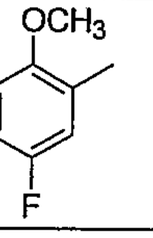
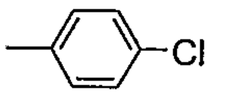
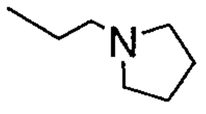
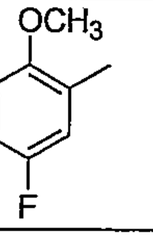
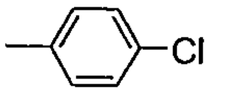
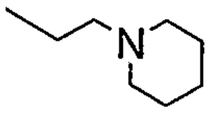
B2			
B3			
B4			
B5			
B6			
B7			
B8			
B9			
B10			 Sulfur is oxidized to Sulfoxide
B11		Et	
B12			
B13			
B14			
B15			
B16			

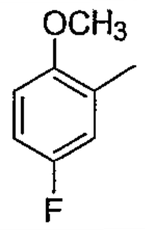
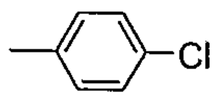
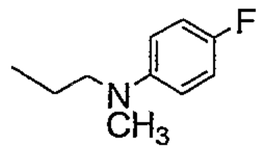
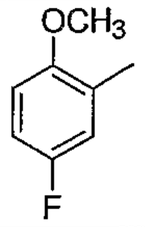
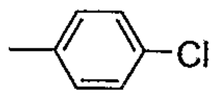
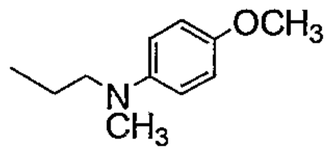
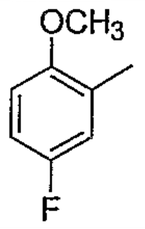
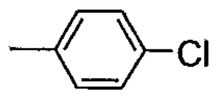
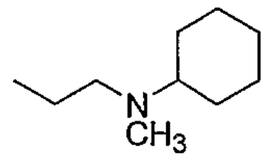
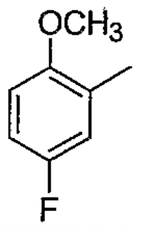
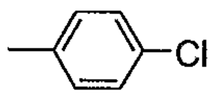
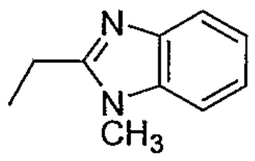
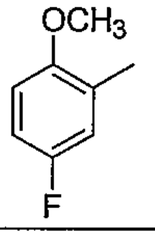
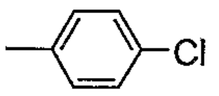
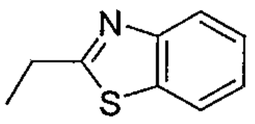
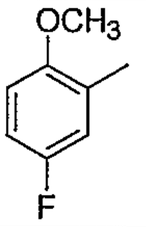
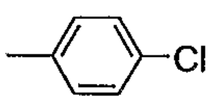
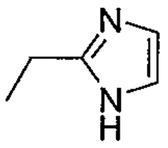
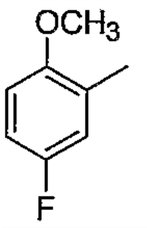
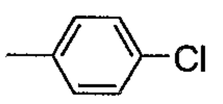
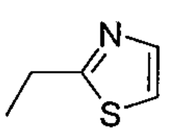
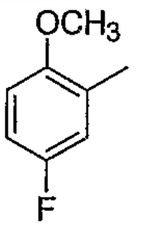
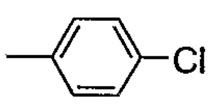
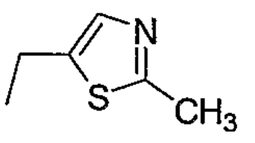
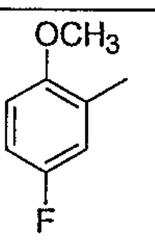
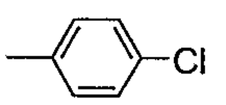
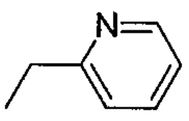
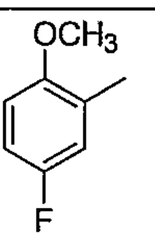
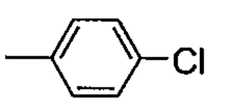
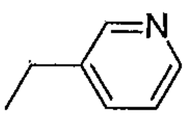
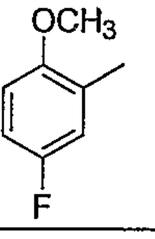
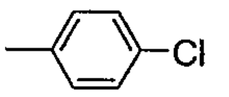
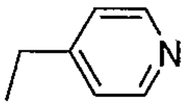
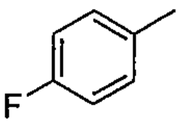
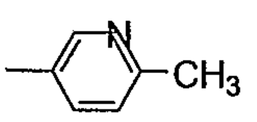
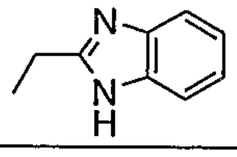
B17			
B18			
B19			
B20			
B21			
B22			
B23			
B24			
B25			
B26			
B27			
B28			
B29			
B30			
B31			
B32			

B33			
B34			
B35			
B36			
B37			
B38			
B39			
B40			
B41			
B42			
B43			
B44			
B45			
B46			
B47			
B48			
B49			
B50			

B51			
B52			
B53			
B54			
B55			
B56			
B57			
B58			
B59			
B60			
B61			
B62			
B63			
B64			
B65			
B66			
B67			
B68			

B69			
B70			
B71			
B72			
B73			
B74			
B75			
B76			
B77			
B78			
B79			
B80			
B81			
B82			

B83			
B84			
B85			
B86			
B87			
B88			
B89			
B90			
B91			
B92			
B93			
B94			

B95			
B96			
B97			
B98			
B99			
B100			
B101			
B102			
B103			
B104			
B105			
B106			

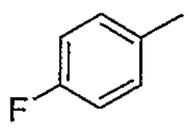
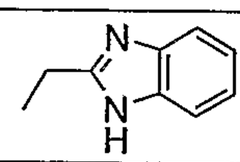
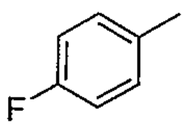
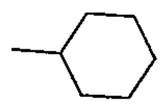
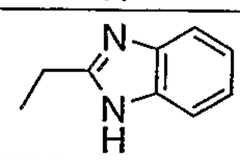
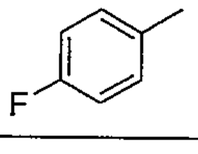
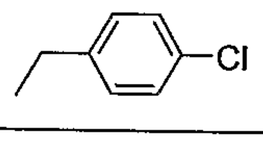
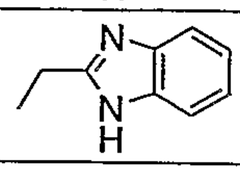
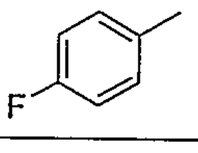
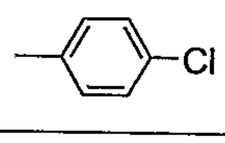
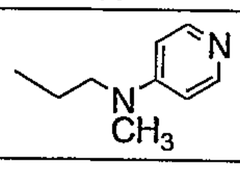
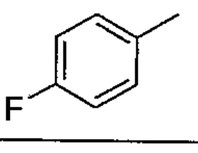
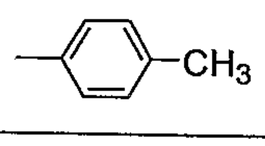
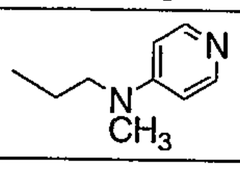
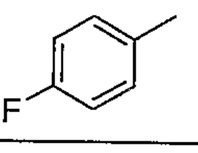
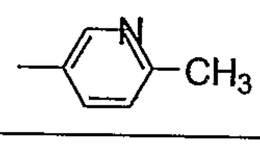
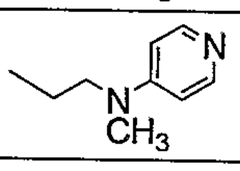
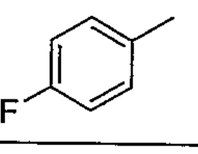
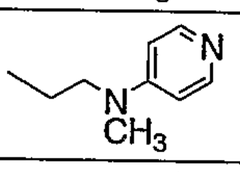
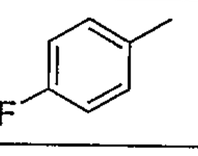
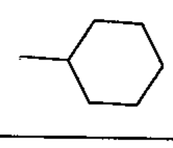
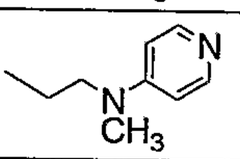
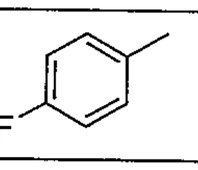
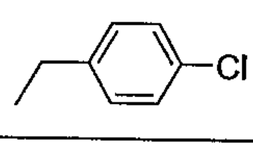
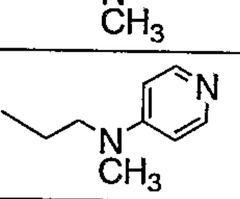
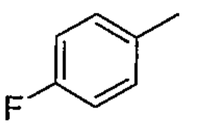
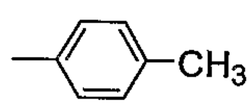
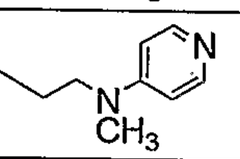
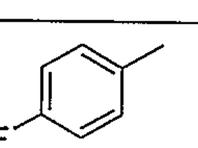
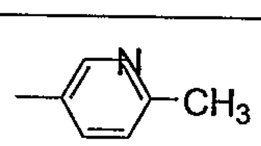
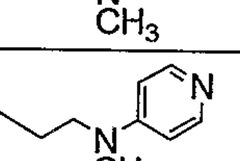
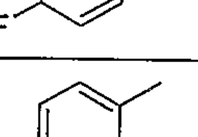
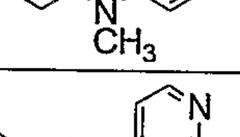
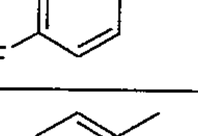
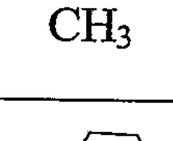
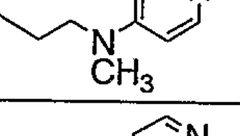
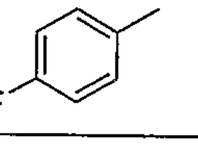
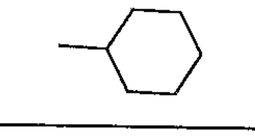
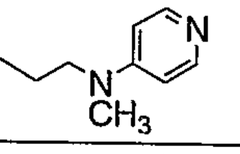
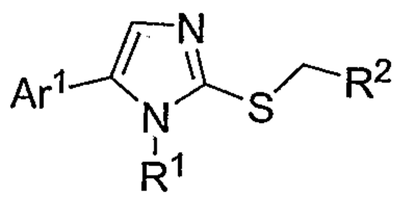
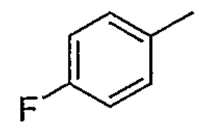
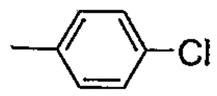
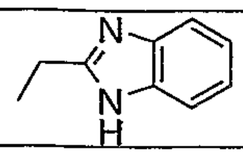
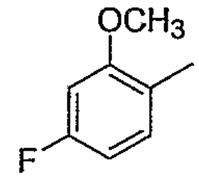
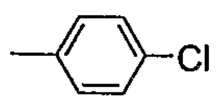
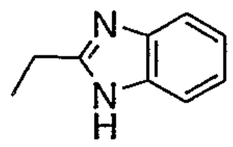
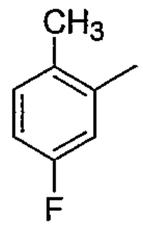
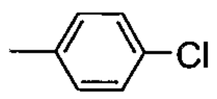
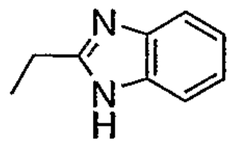
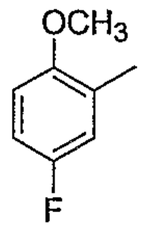
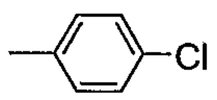
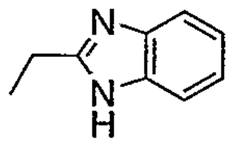
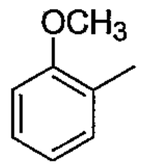
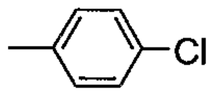
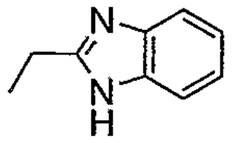
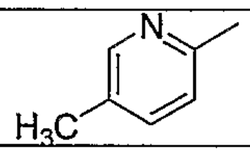
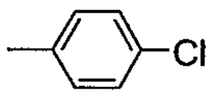
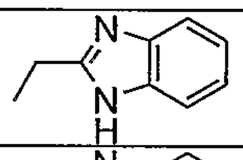
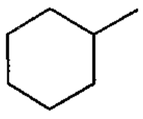
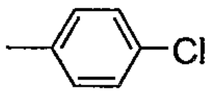
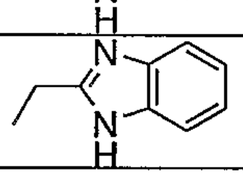
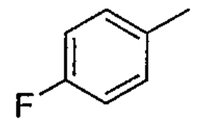
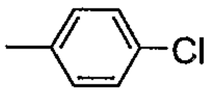
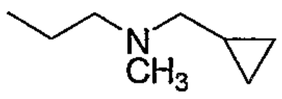
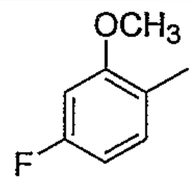
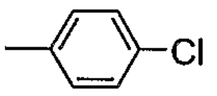
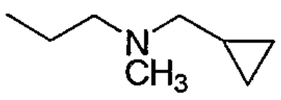
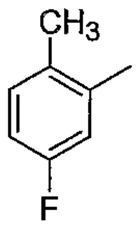
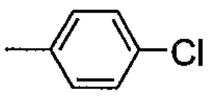
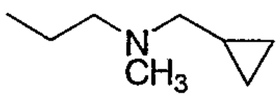
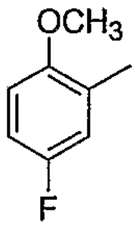
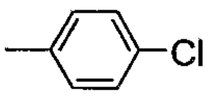
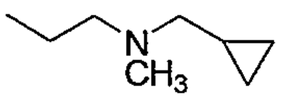
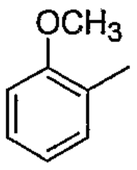
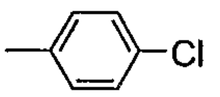
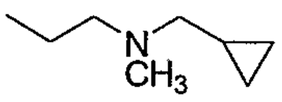
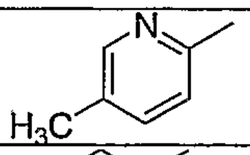
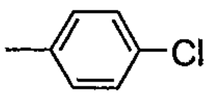
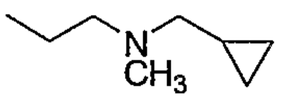
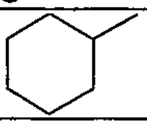
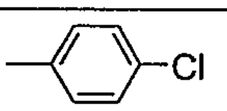
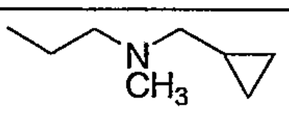
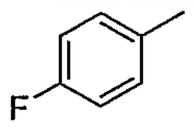
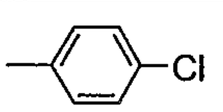
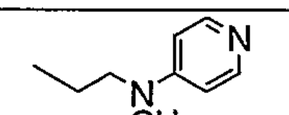
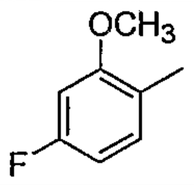
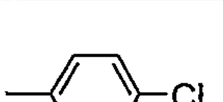
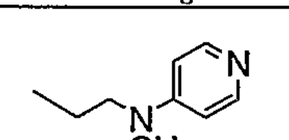
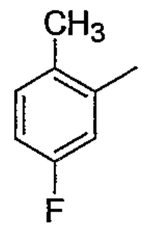
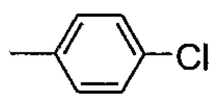
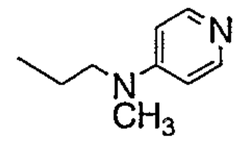
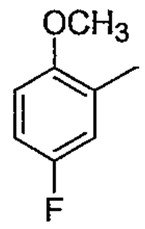
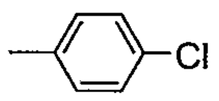
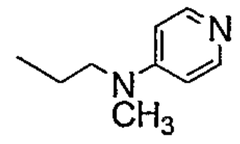
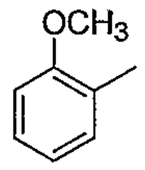
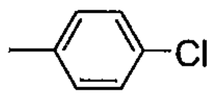
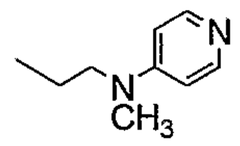
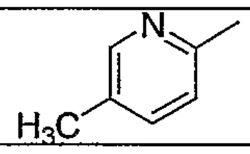
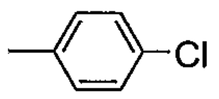
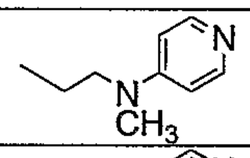
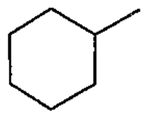
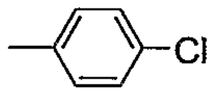
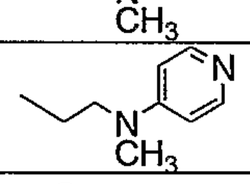
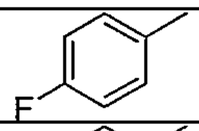
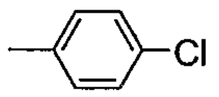
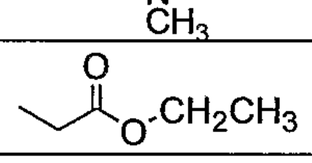
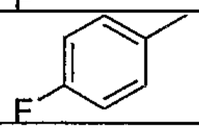
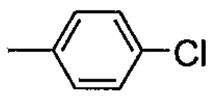
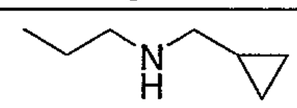
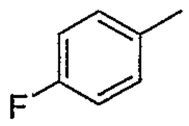
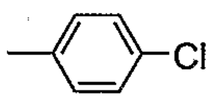
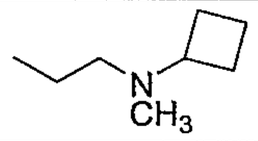
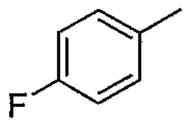
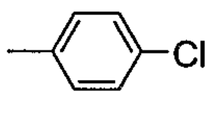
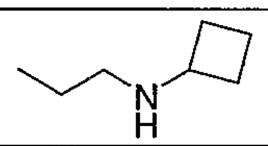
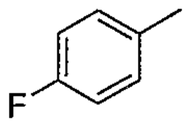
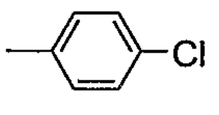
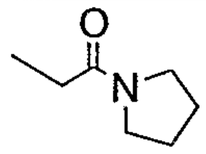
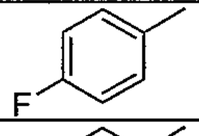
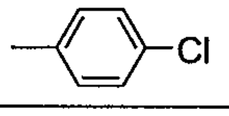
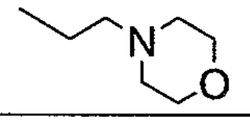
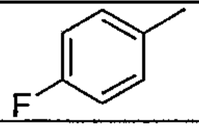
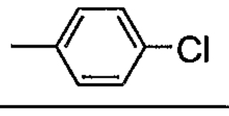
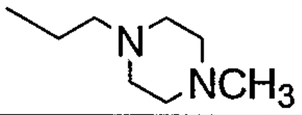
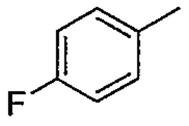
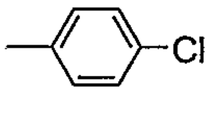
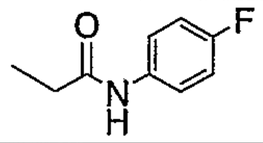
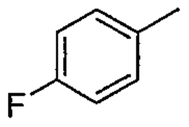
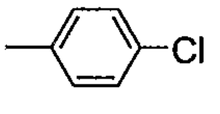
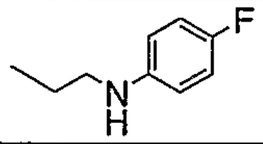
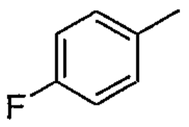
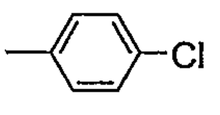
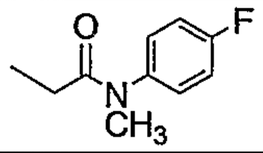
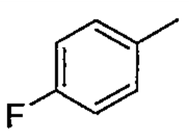
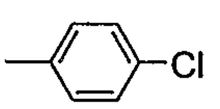
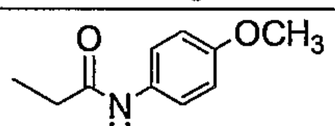
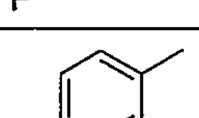
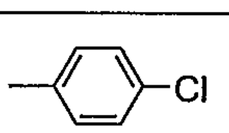
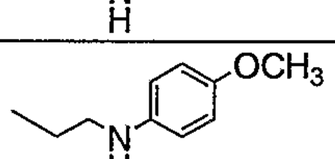
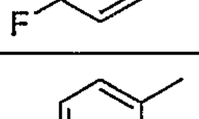
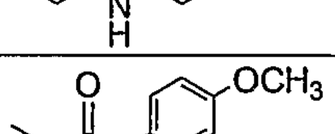
B107		CH_3	
B108			
B109			
B110			
B111			
B112			
B113		CH_3	
B114			
B115			
B116			
B117			
B118		CH_3	
B119			
B120			

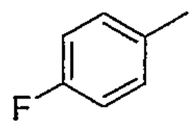
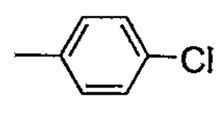
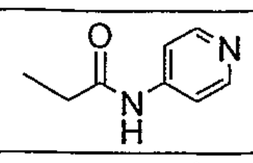
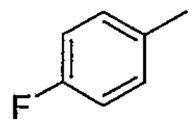
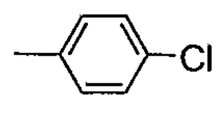
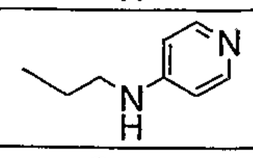
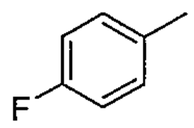
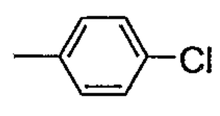
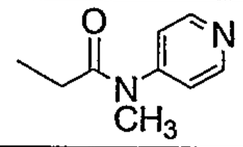
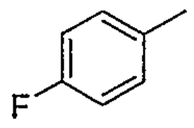
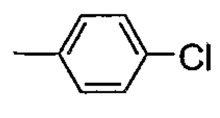
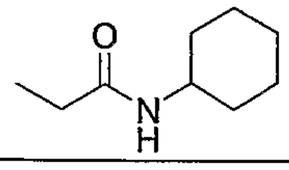
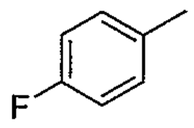
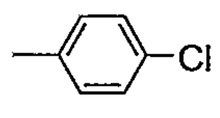
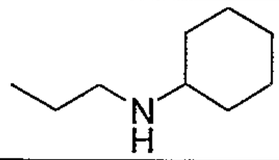
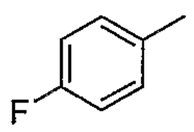
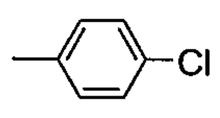
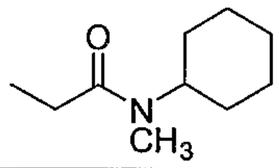
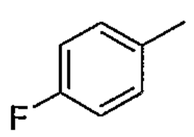
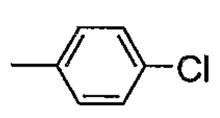
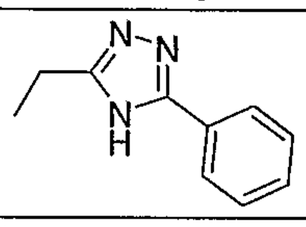
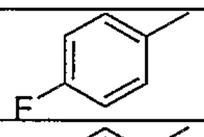
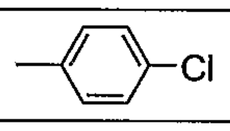
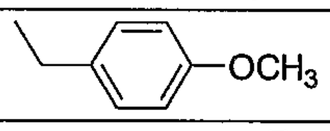
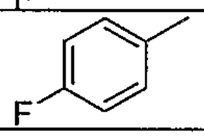
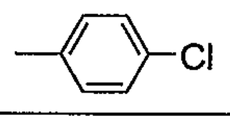
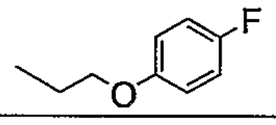
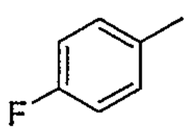
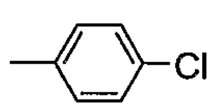
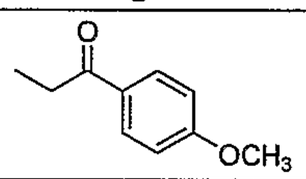
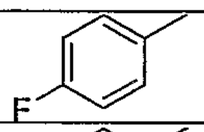
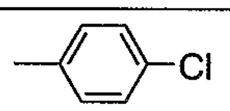
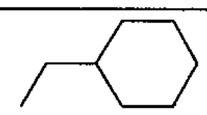
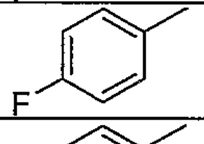
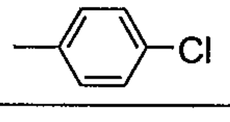
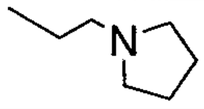
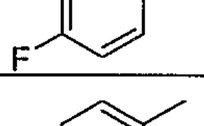
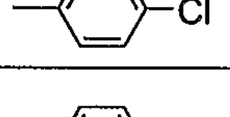
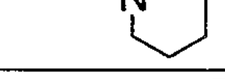
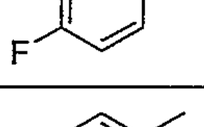
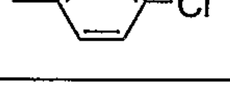
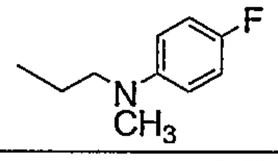
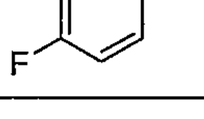
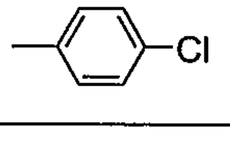
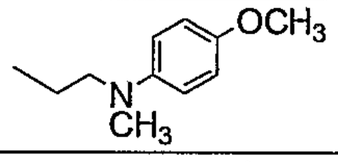
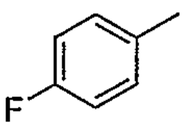
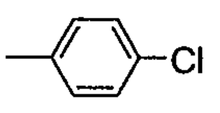
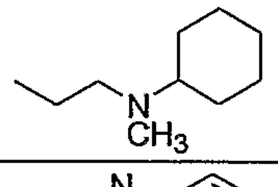
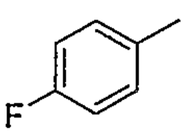
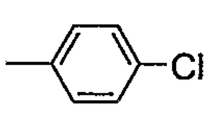
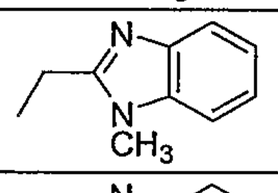
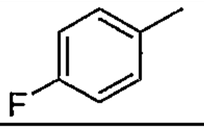
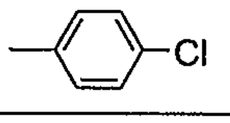
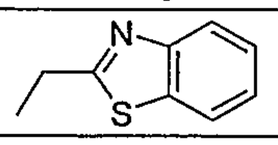
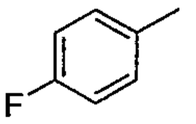
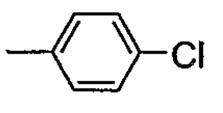
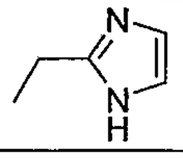
TABLE B1B

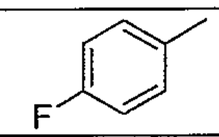
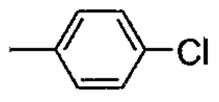
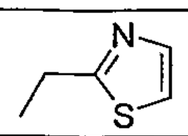
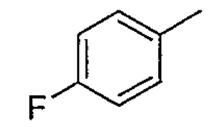
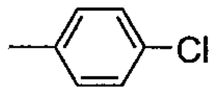
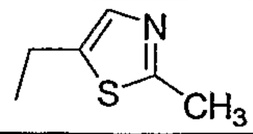
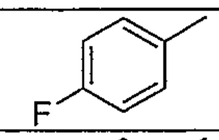
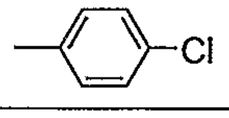
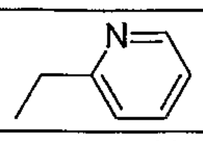
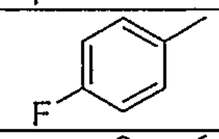
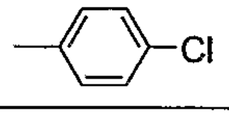
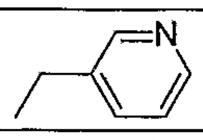
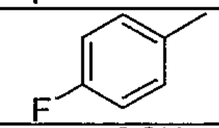
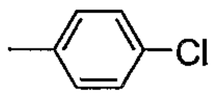
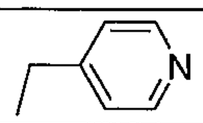
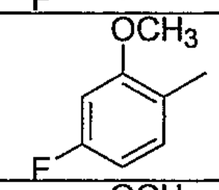
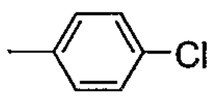
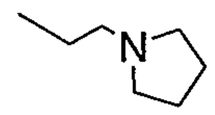
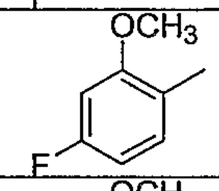
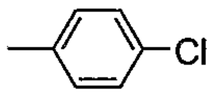
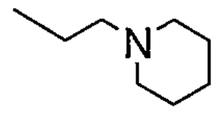
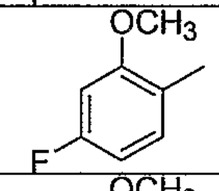
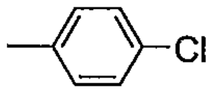
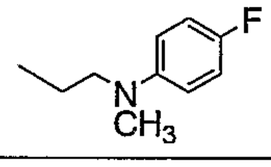
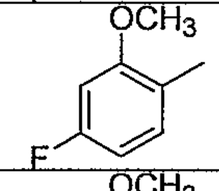
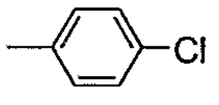
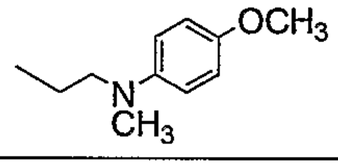
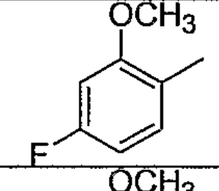
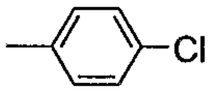
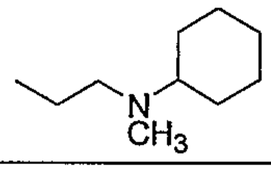
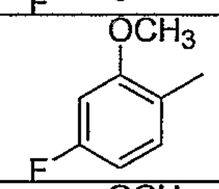
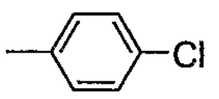
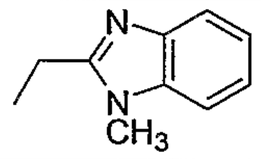
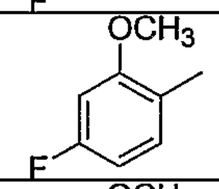
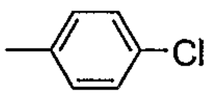
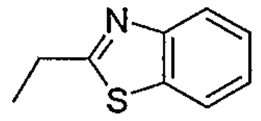
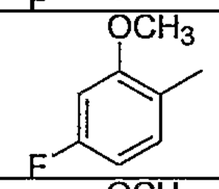
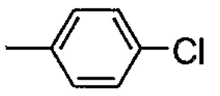
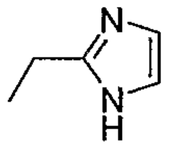
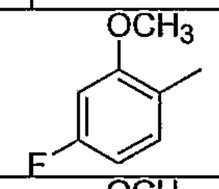
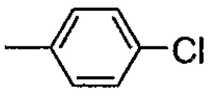
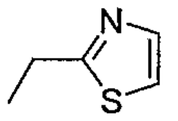
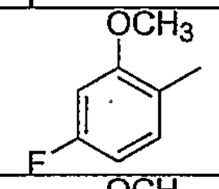
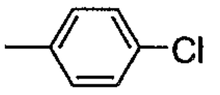
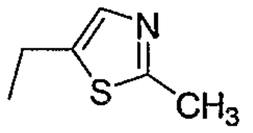
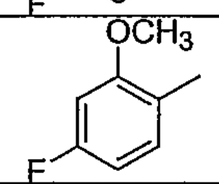
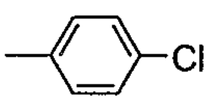
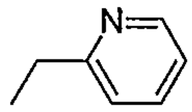
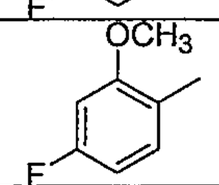
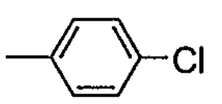
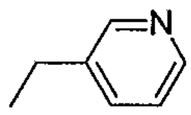
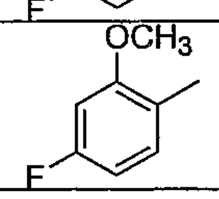
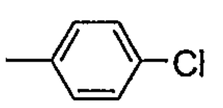
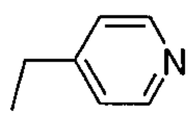


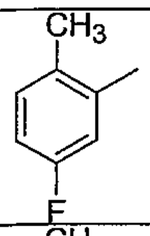
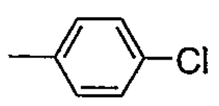
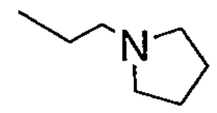
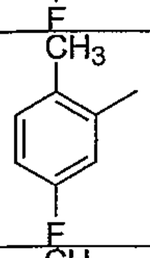
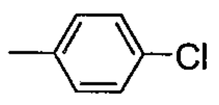
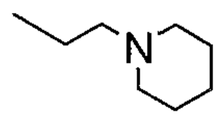
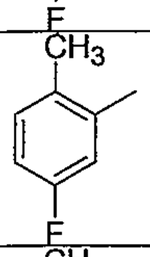
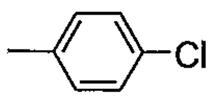
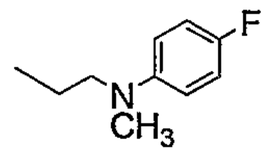
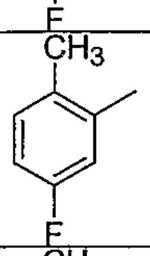
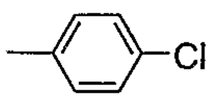
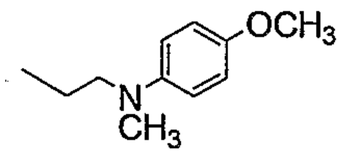
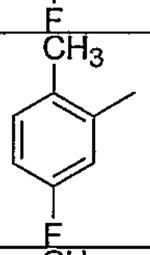
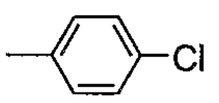
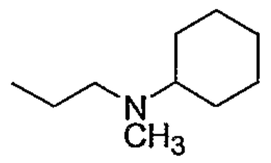
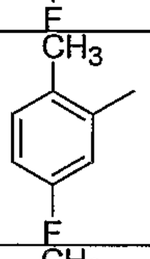
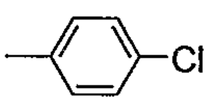
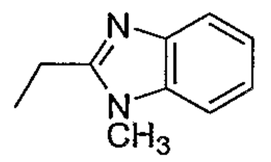
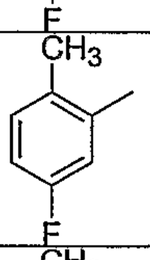
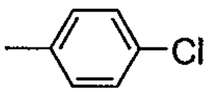
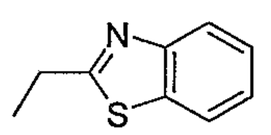
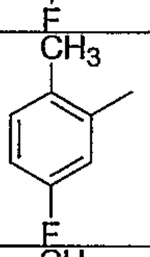
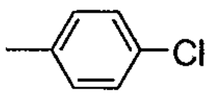
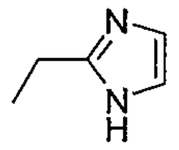
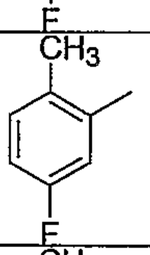
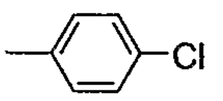
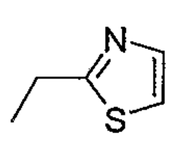
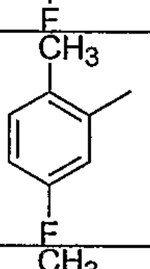
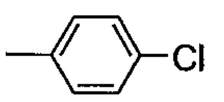
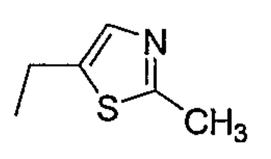
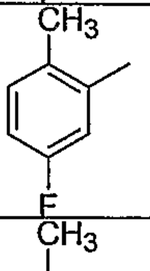
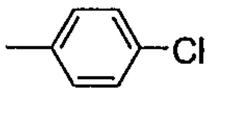
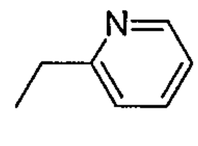
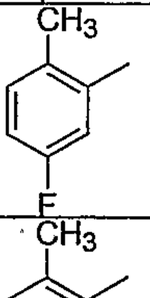
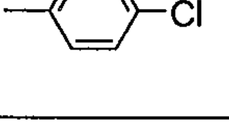
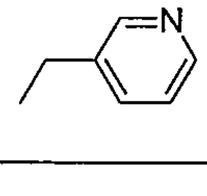
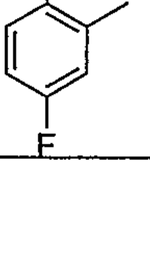
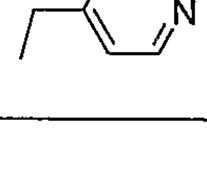
Cpd No.	Ar^1	R^1	R^2

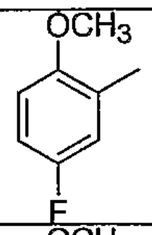
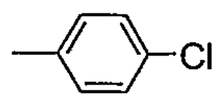
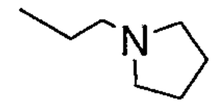
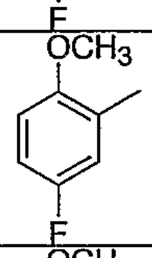
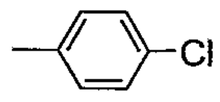
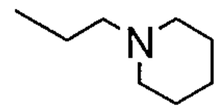
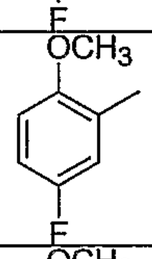
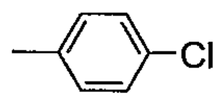
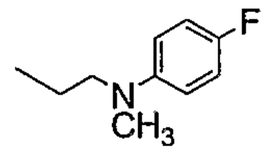
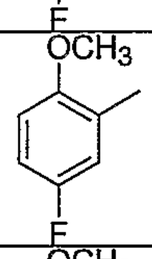
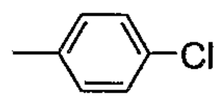
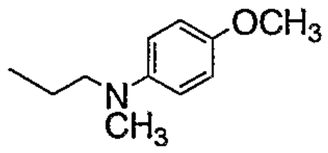
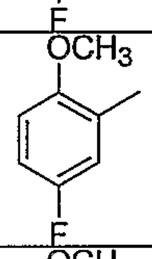
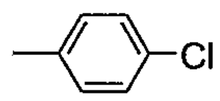
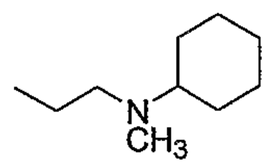
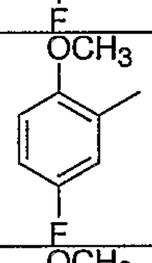
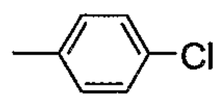
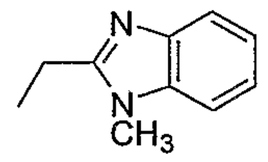
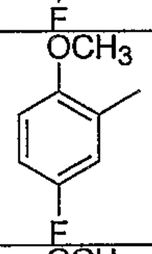
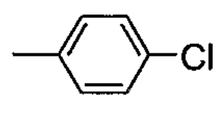
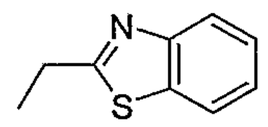
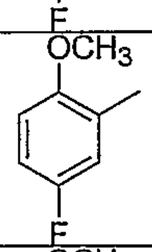
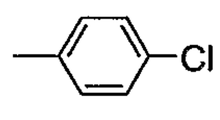
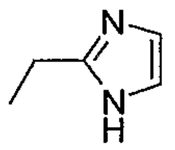
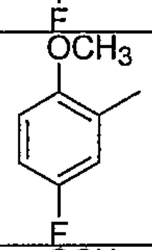
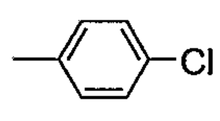
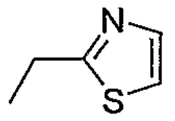
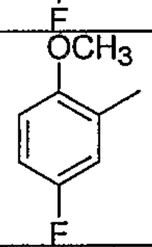
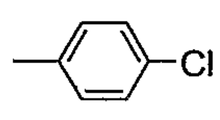
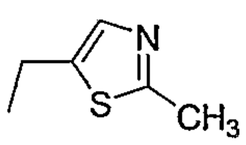
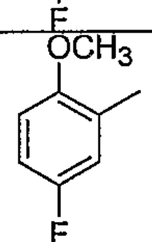
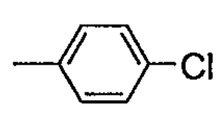
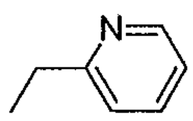
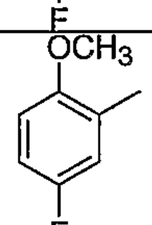
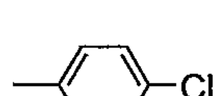
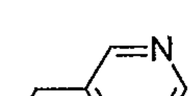
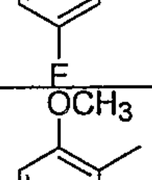
B121			
B122			
B123			
B124			
B125			
B126			
B127			
B128			
B129			
B130			
B131			
B132			
B133			
B134			
B135			
B136			

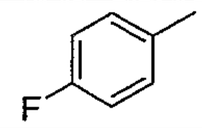
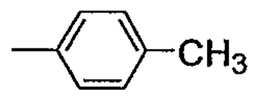
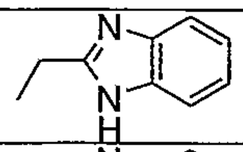
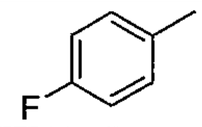
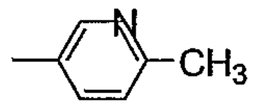
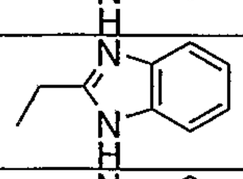
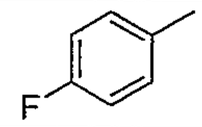
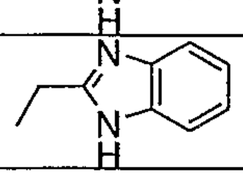
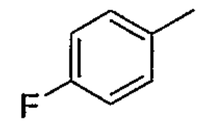
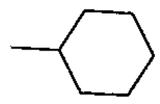
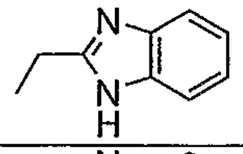
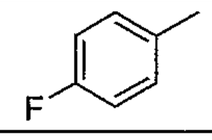
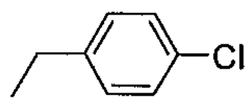
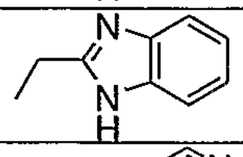
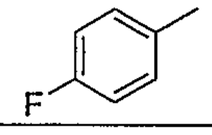
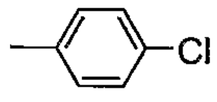
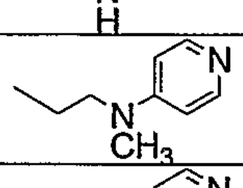
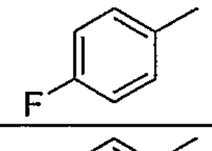
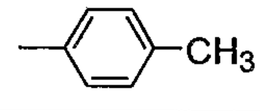
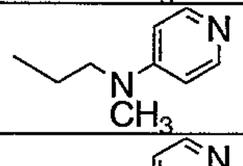
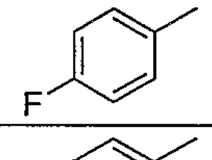
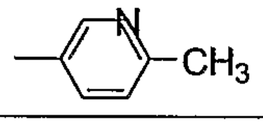
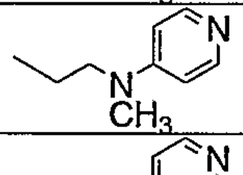
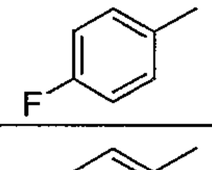
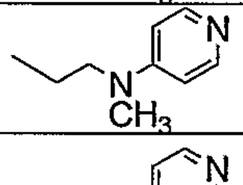
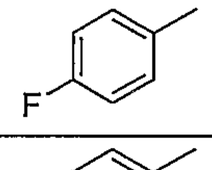
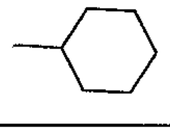
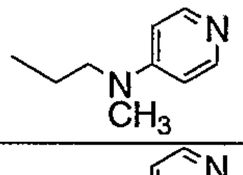
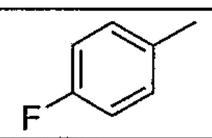
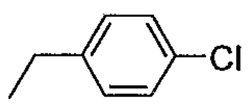
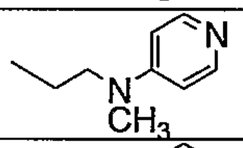
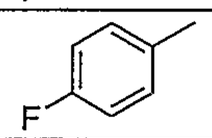
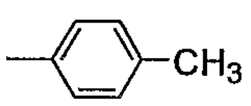
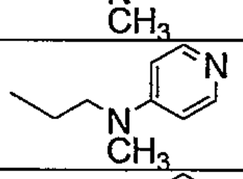
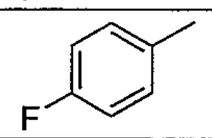
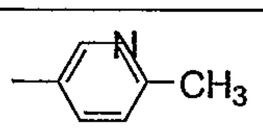
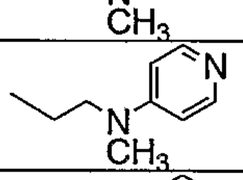
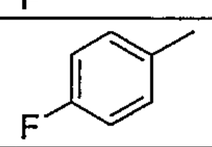
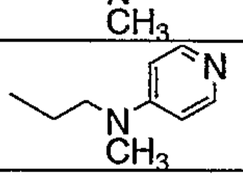
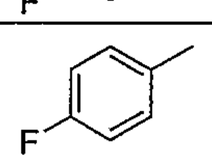
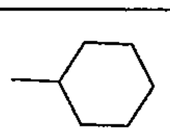
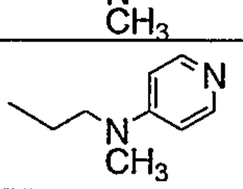
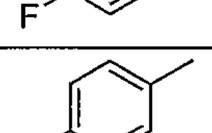
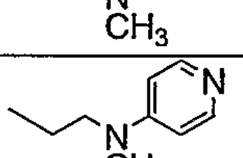
B137			
B138			
B139			
B140			
B141			
B142			
B143			
B144			
B145			
B146			
B147			
B148			
B149			
B150			
B151			
B152			
B153			
B154			

B155			
B156			
B157			
B158			
B159			
B160			
B161			
B162			
B163			
B164			
B165			
B166			
B167			
B168			
B169			
B170			
B171			
B172			
B173			

B174			
B175			
B176			
B177			
B178			
B179			
B180			
B181			
B182			
B183			
B184			
B185			
B186			
B187			
B188			
B189			
B190			
B191			

B192			
B193			
B194			
B195			
B196			
B197			
B198			
B199			
B200			
B201			
B202			
B203			
B204			

B205			
B206			
B207			
B208			
B209			
B210			
B211			
B212			
B213			
B214			
B215			
B216			
B217			

B218			
B219			
B220		CH_3	
B221			
B222			
B223			
B224			
B225			
B226		CH_3	
B227			
B228			
B229			
B230			
B231		CH_3	
B232			
B233			

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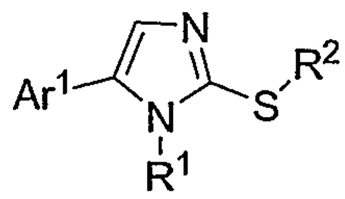
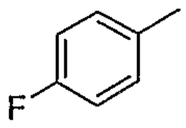
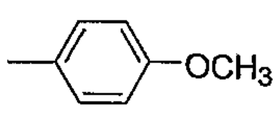
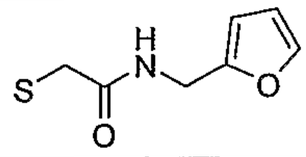
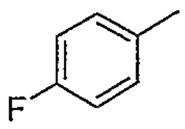
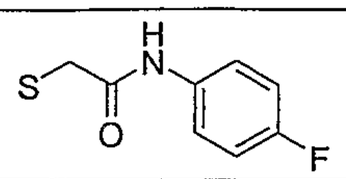
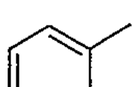
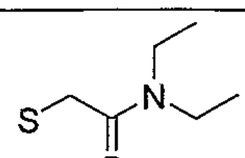
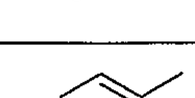
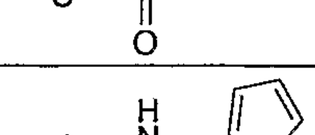
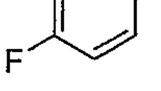
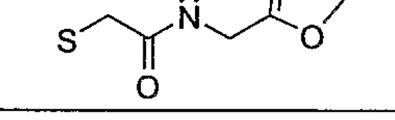
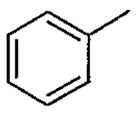
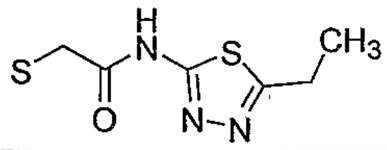
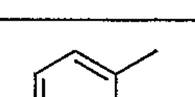
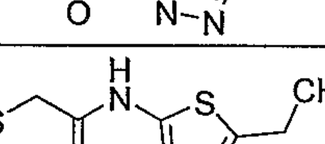
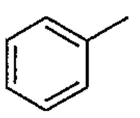
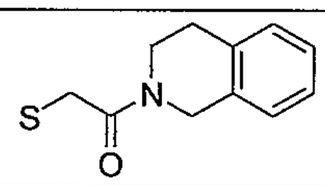
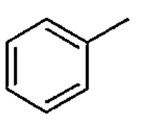
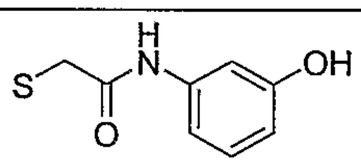
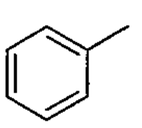
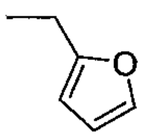
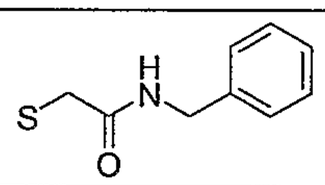
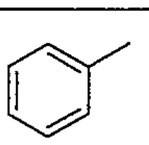
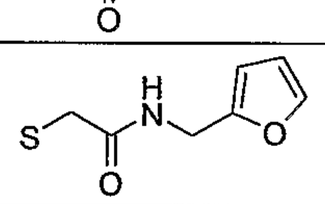
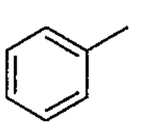
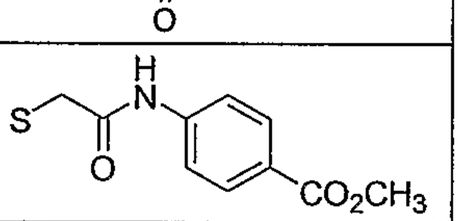
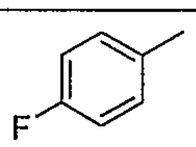
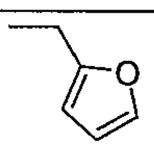
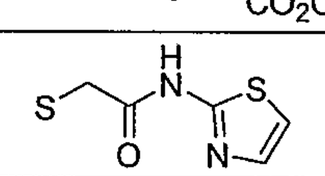
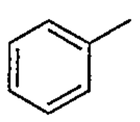
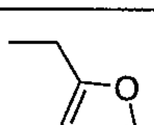
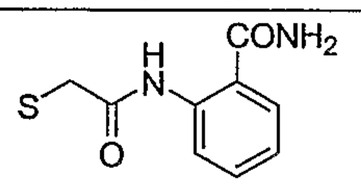
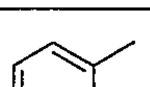
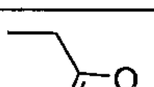
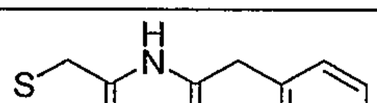
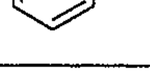
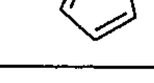
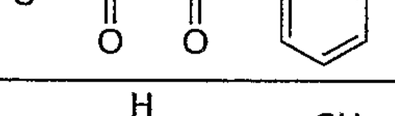
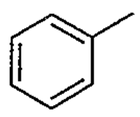
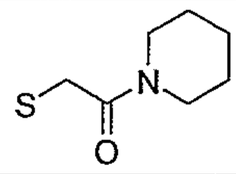
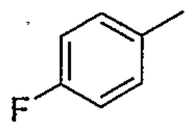
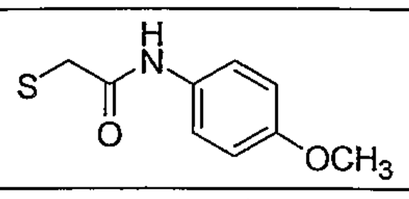
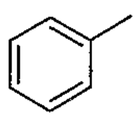
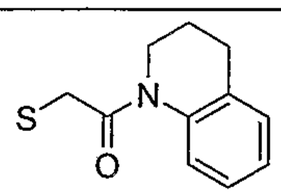
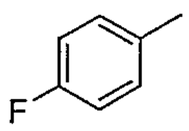
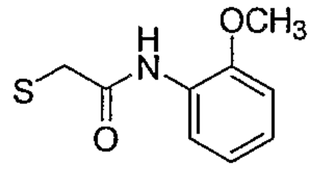
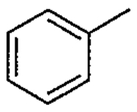
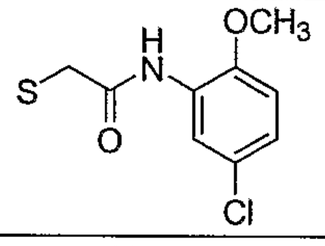
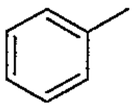
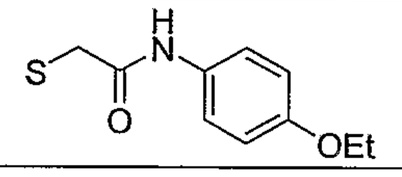
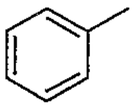
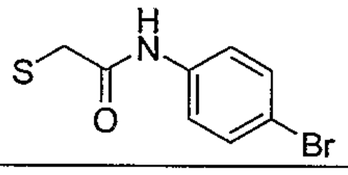
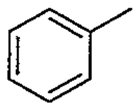
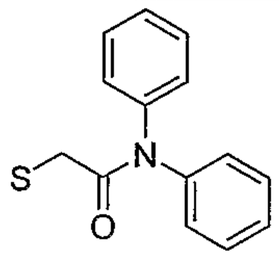
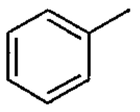
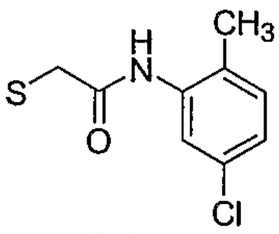
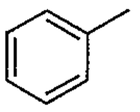
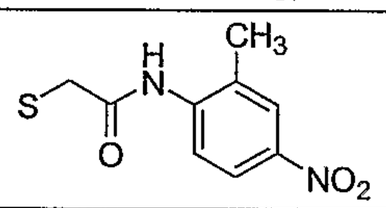
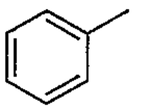
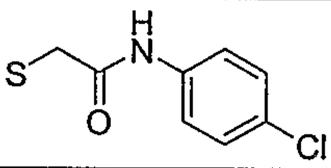
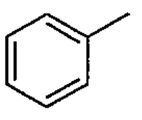
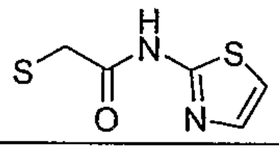
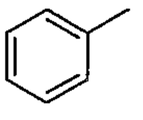
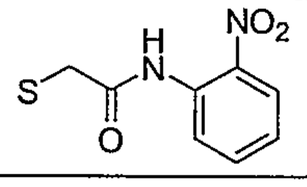
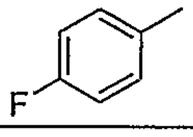
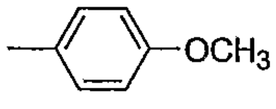
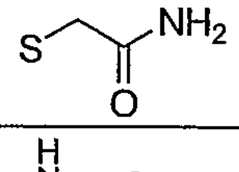
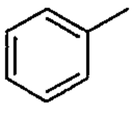
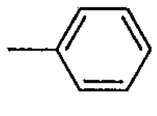
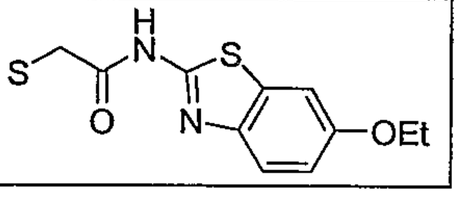
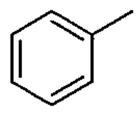
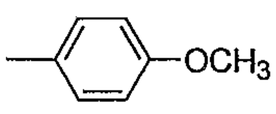
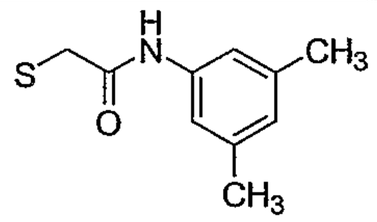
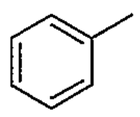
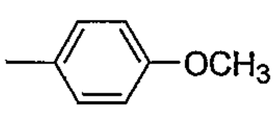
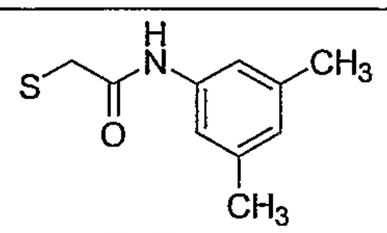
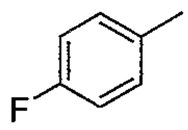
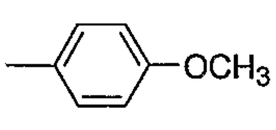
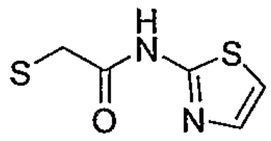


Cpd No.	Ar^1	R^1	R^2

B234			
B235		CH_3	
B236		CH_3	
B237		CH_3	
B238		CH_3	
B239		Et	
B240		CH_3	
B241		CH_3	
B242		CH_3	
B243			
B244		CH_3	
B245		CH_3	
B246			
B247			
B248			
B249			

B250		CH_3	
B251		CH_3	
B252		Et	
B253		CH_3	
B254		CH_3	
B255		CH_3	
B256		CH_3	
B257		CH_3	
B258		CH_3	
B259		CH_3	
B260		CH_3	
B261		Et	
B262		CH_3	
B263			
B264			

B265			
B266			
B267			

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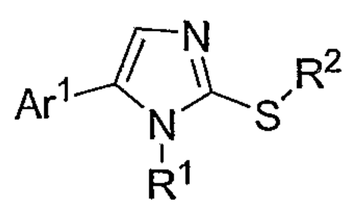

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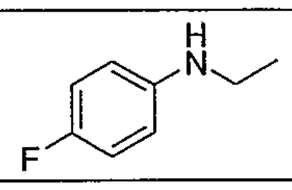
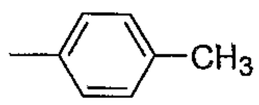
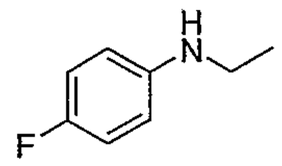
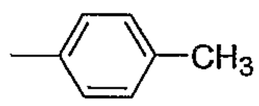
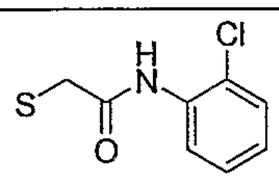
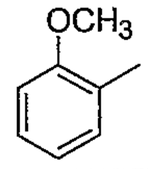
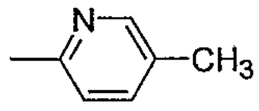
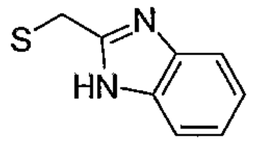
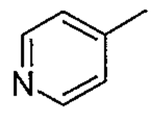
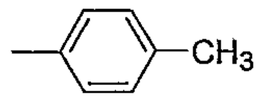
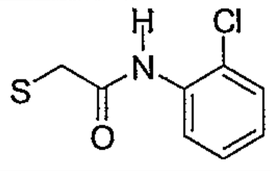
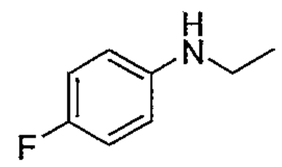
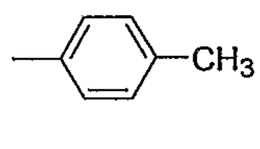
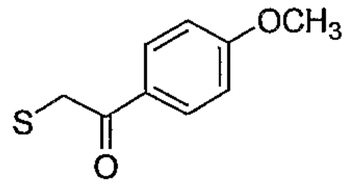
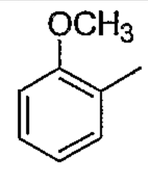
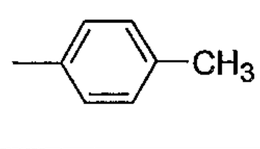
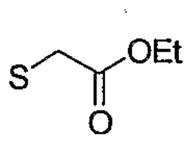
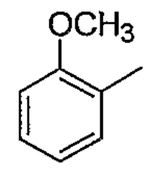
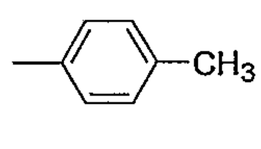
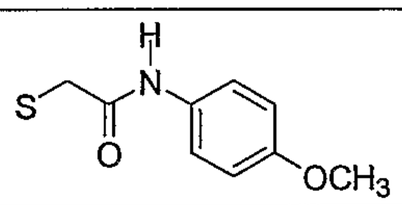
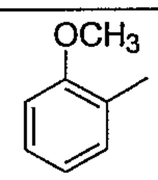
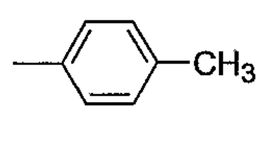
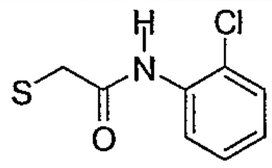
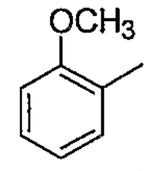
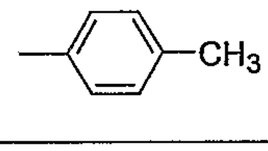
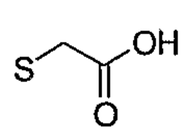
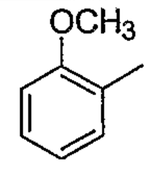
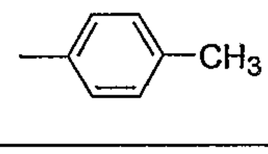
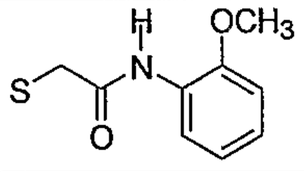
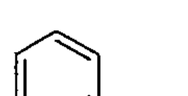
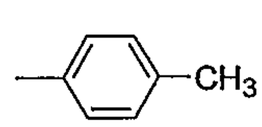
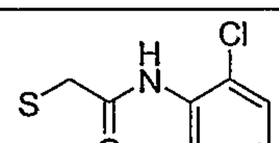
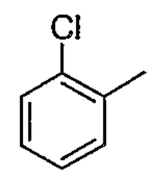
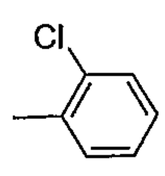
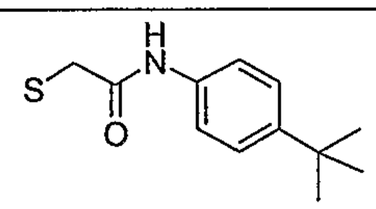
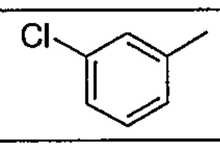
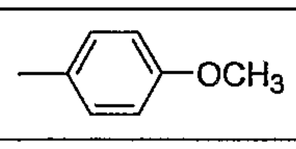
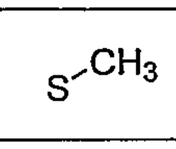
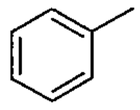
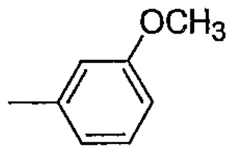
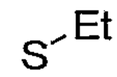
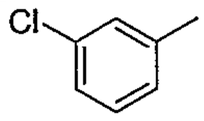
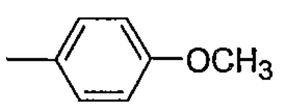
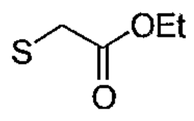
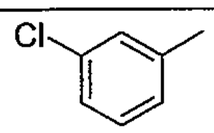
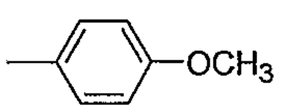
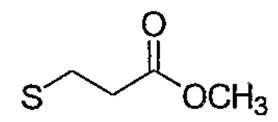
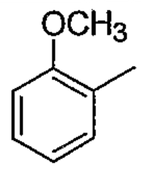
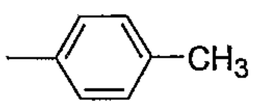
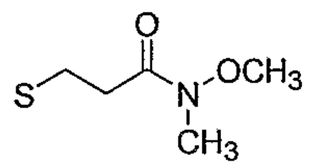
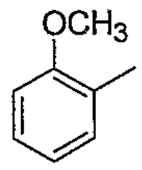
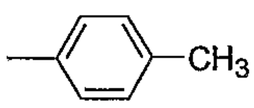
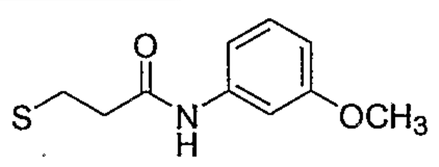
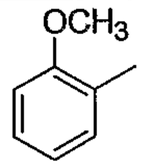
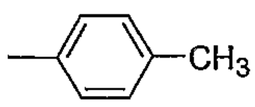
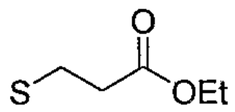
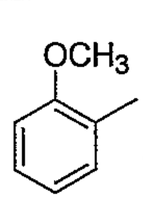
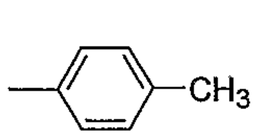
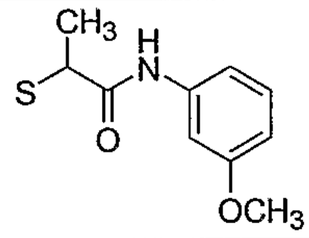
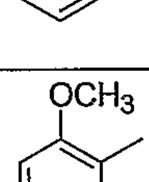
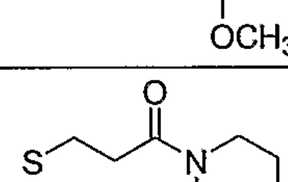
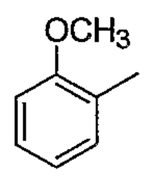
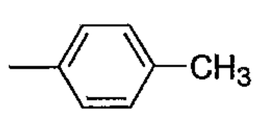
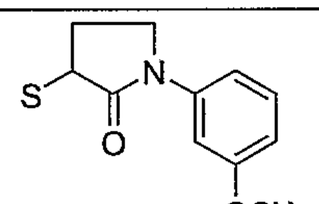
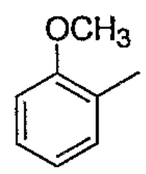
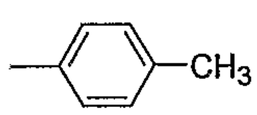
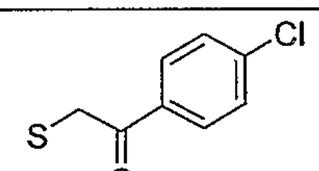
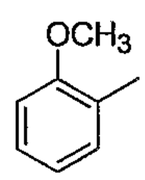
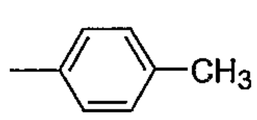
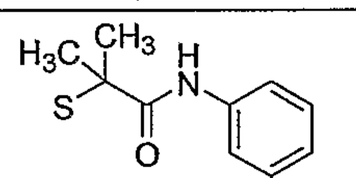
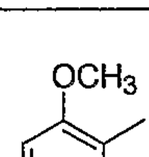
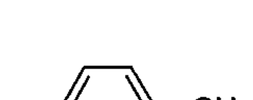
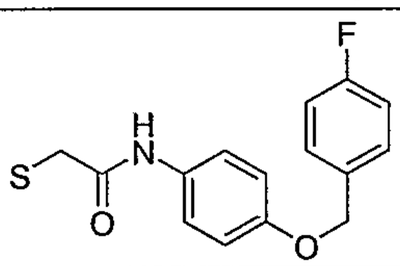
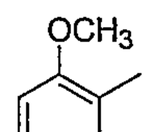
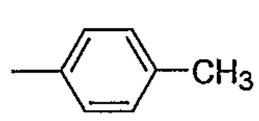
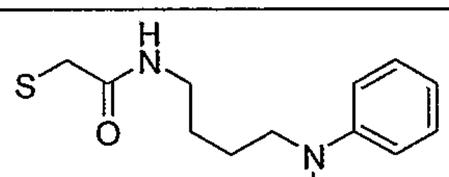
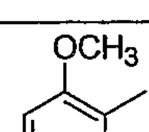
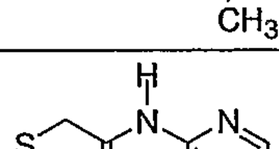
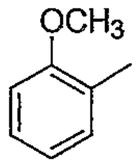
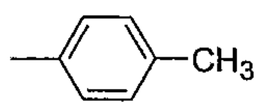
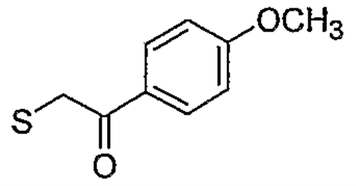
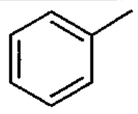
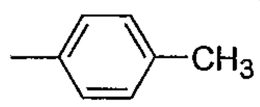
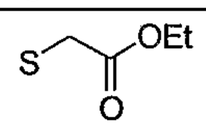
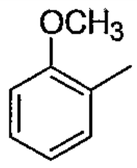
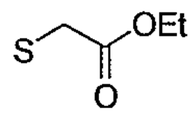
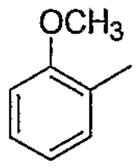
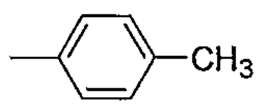
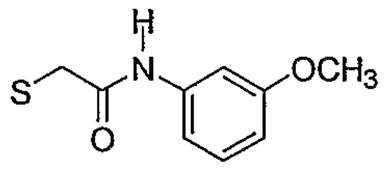
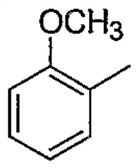
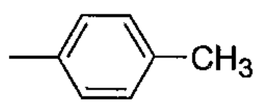
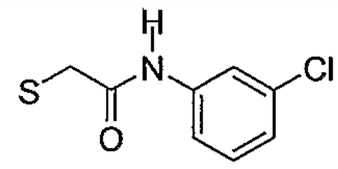
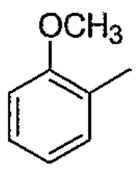
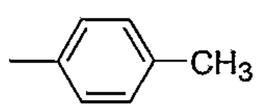
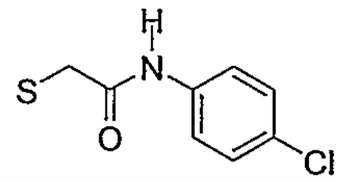
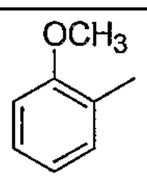
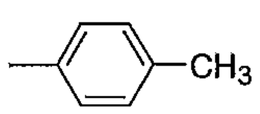
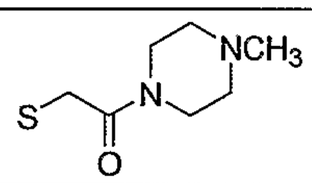
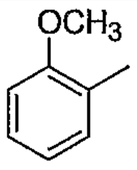
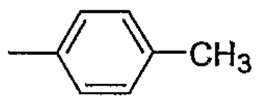
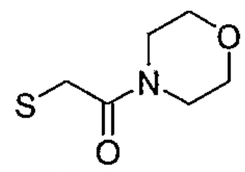
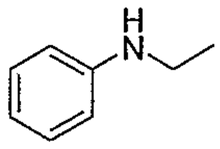
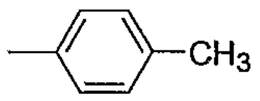
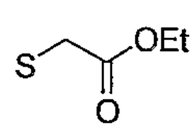
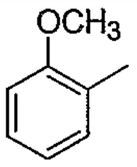
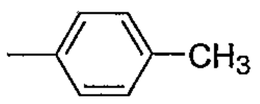
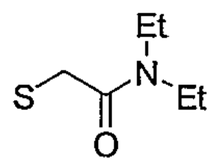
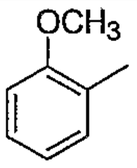
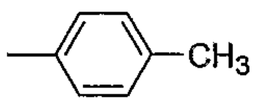
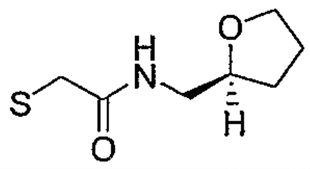
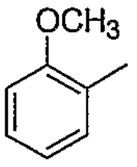
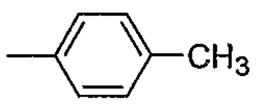
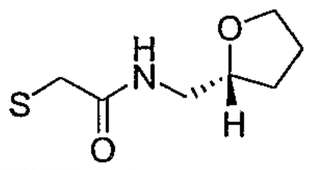
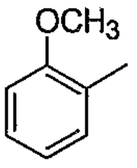
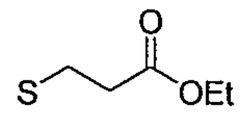
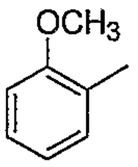
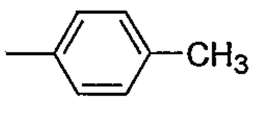
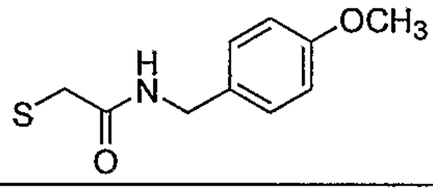
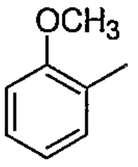
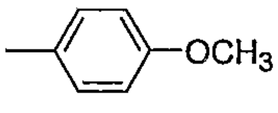
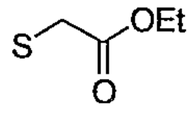
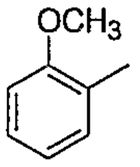
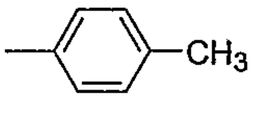
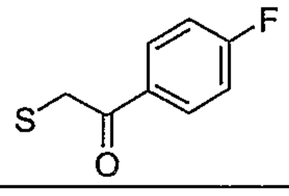
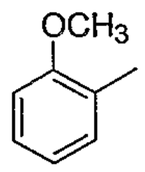
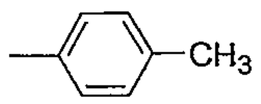
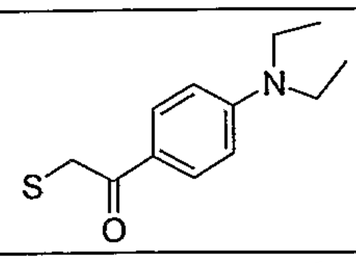
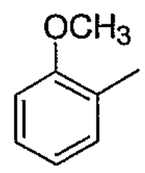
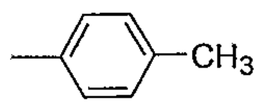
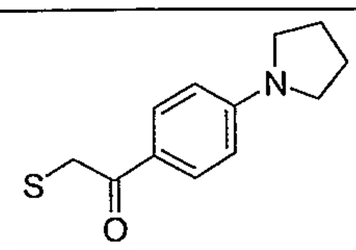
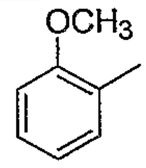
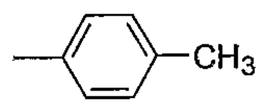
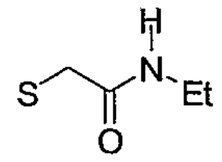
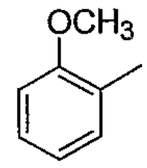
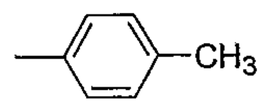
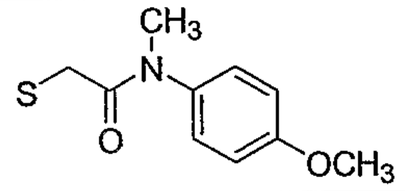
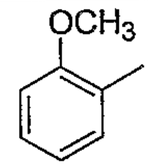
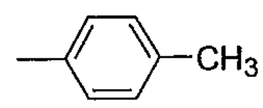
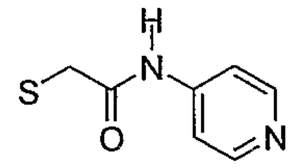
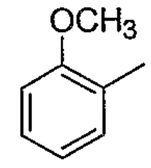
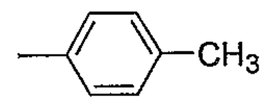
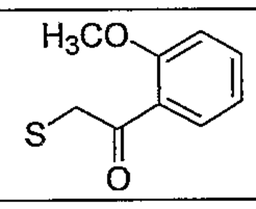
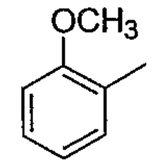
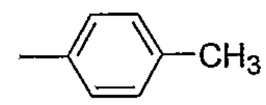
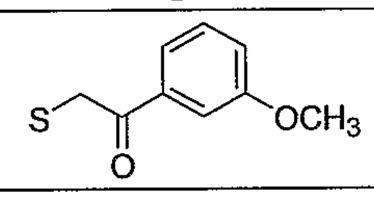
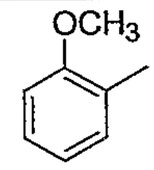
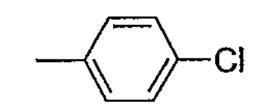
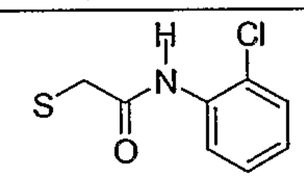
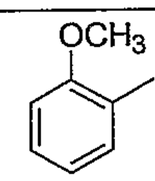
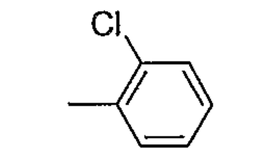
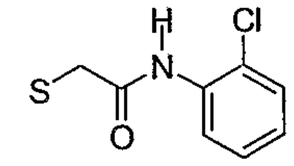
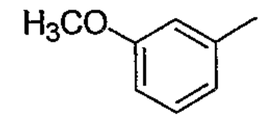
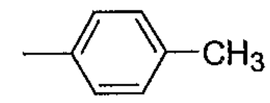
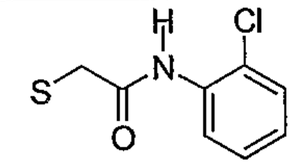
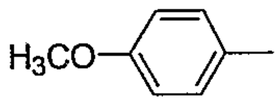
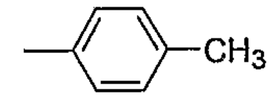
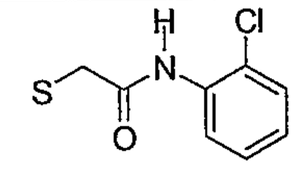
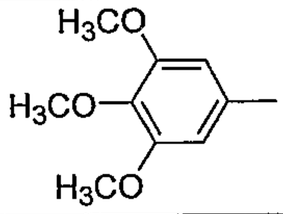
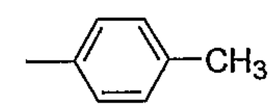
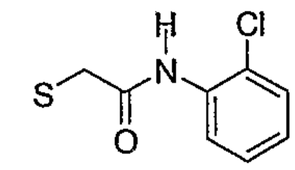
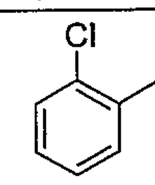
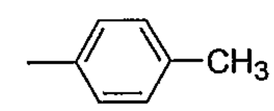
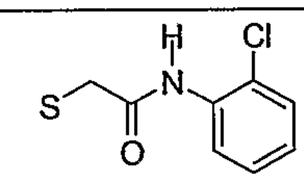
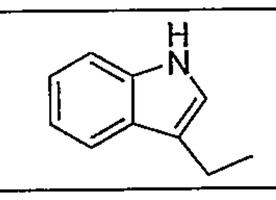
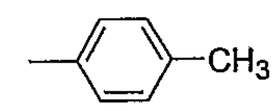
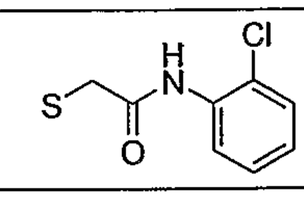
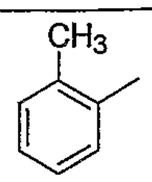
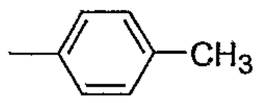
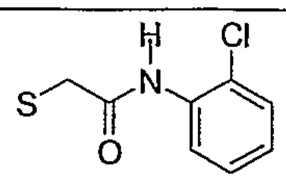
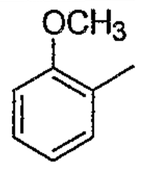
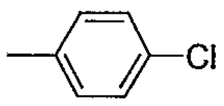
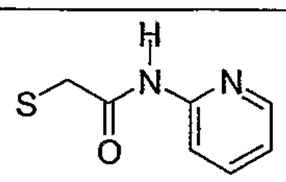
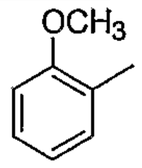
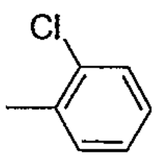
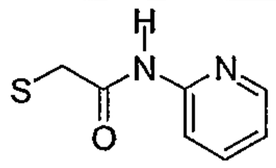
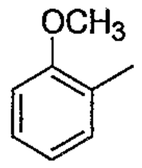
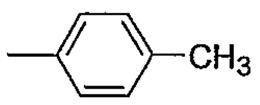
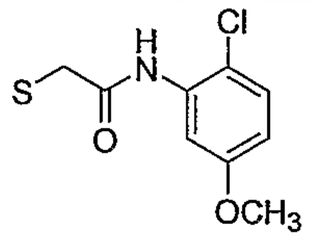
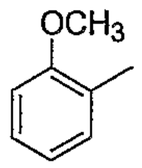
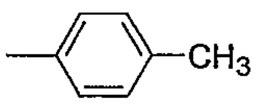
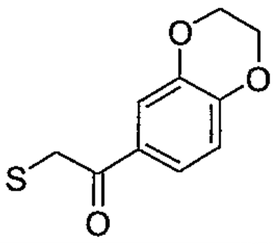
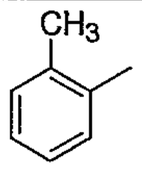
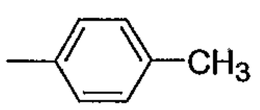
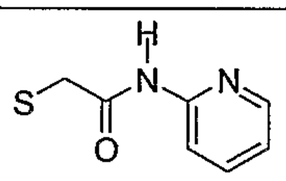
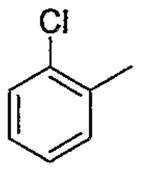
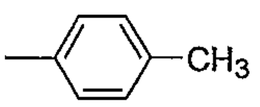
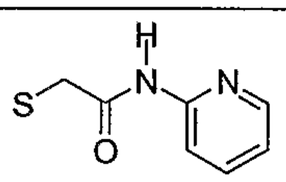
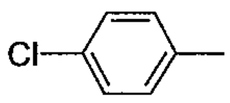
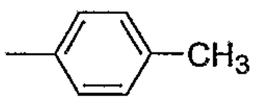
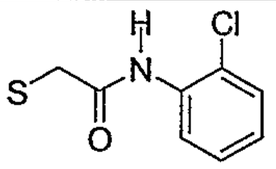
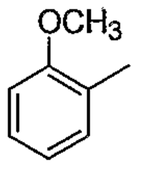
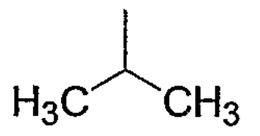
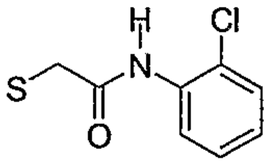
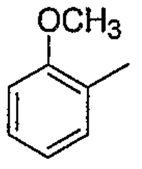
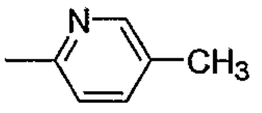
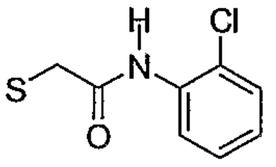
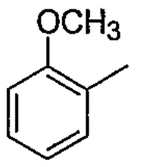
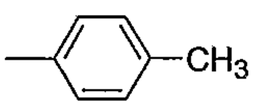
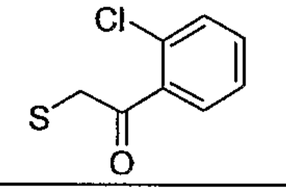
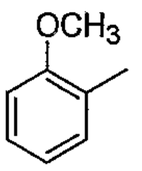
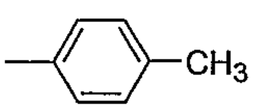
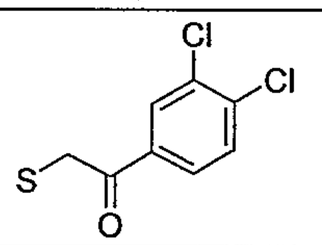
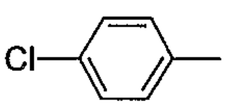
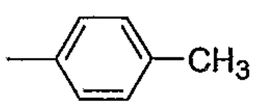
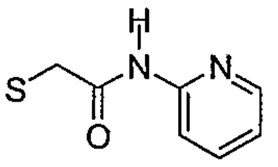
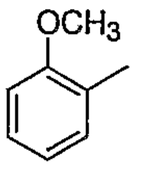
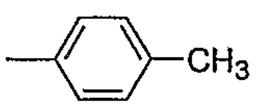
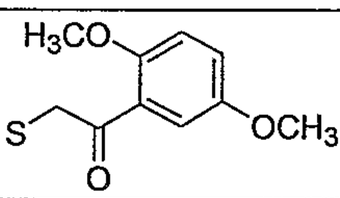
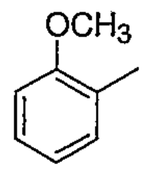
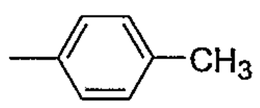
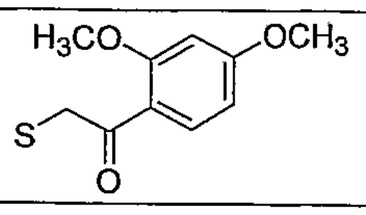
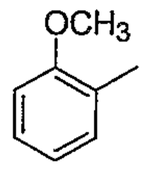
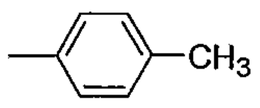
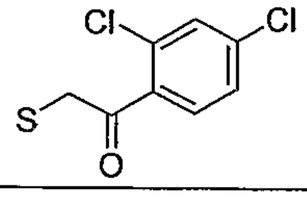
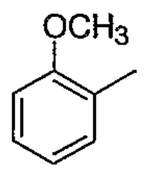
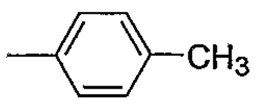
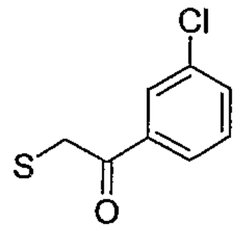
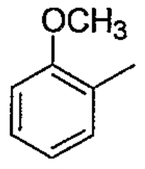
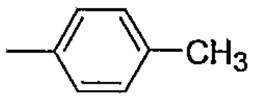
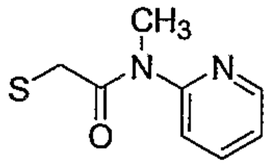
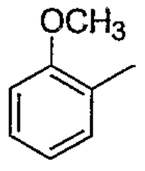
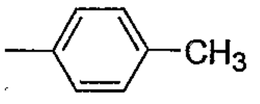
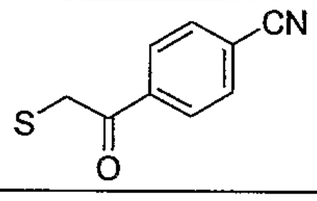
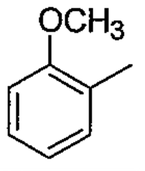
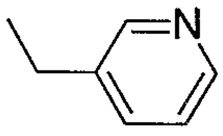
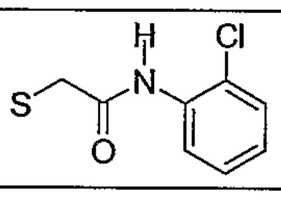
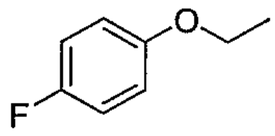
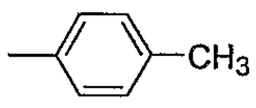
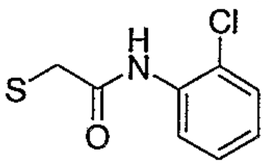
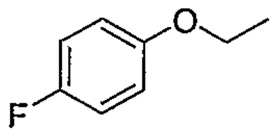
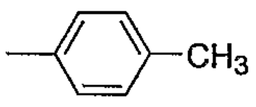
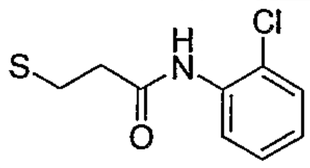
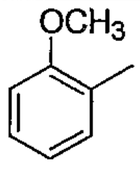
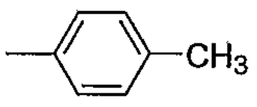
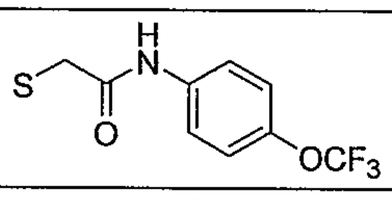
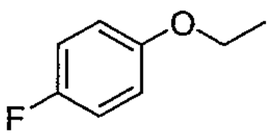
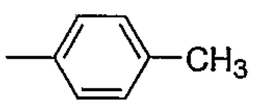
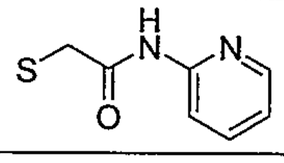
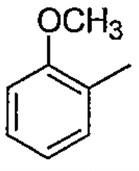
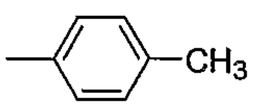
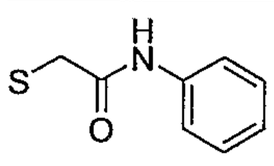
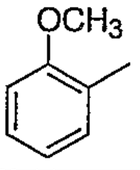
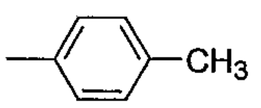
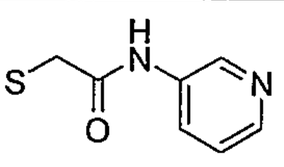
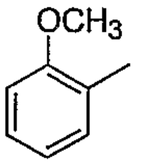
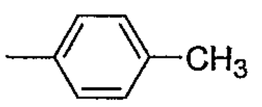
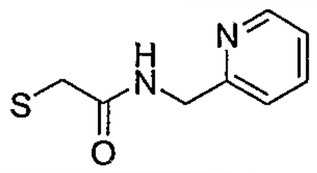
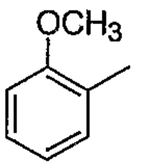
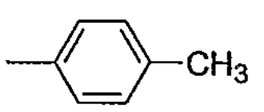
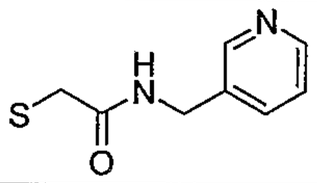
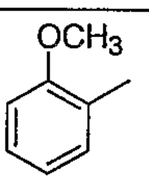
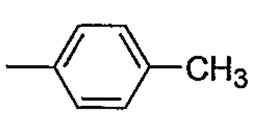
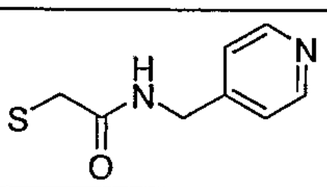
C1			
C2			
C3			
C4			
C5			
C6			
C7			
C8			
C9			
C10			
C11			
C12			
C13			

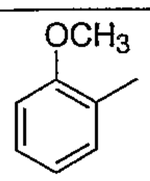
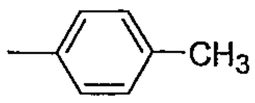
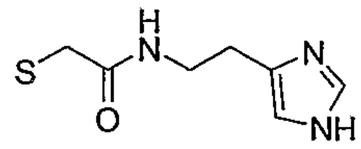
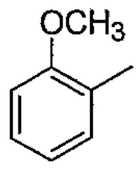
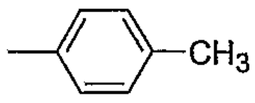
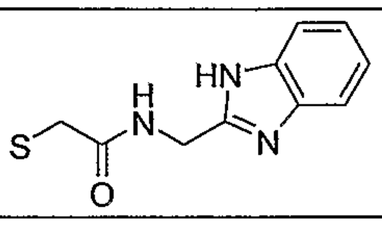
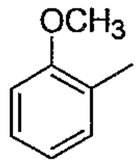
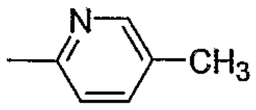
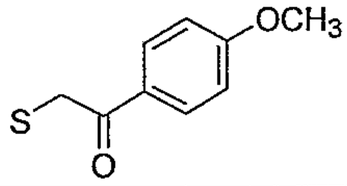
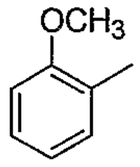
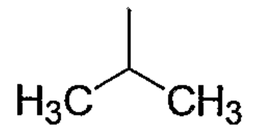
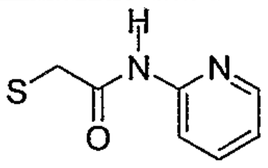
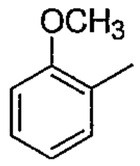
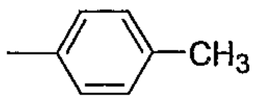
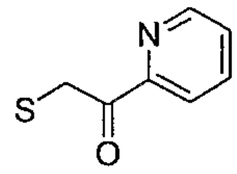
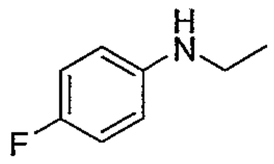
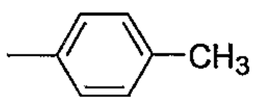
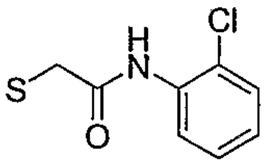
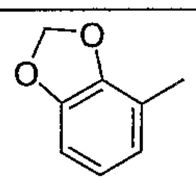
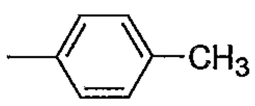
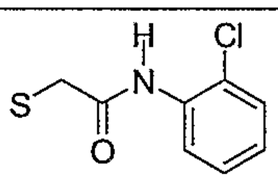
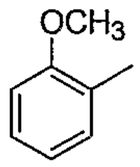
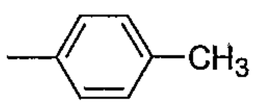
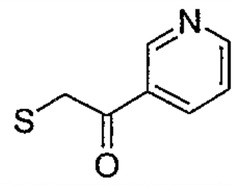
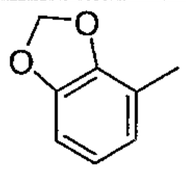
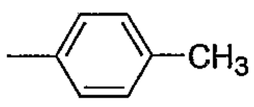
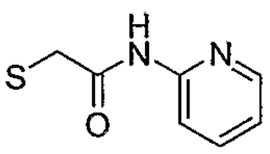
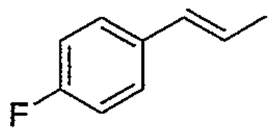
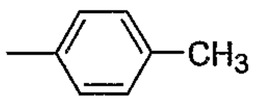
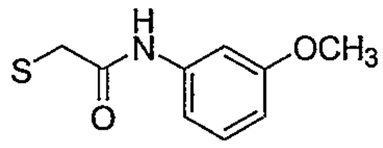
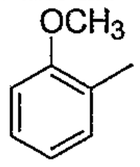
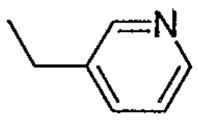
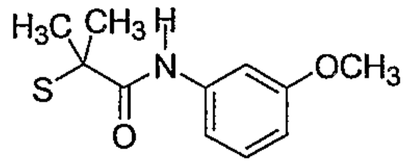
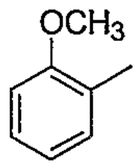
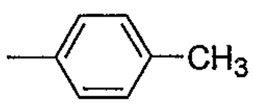
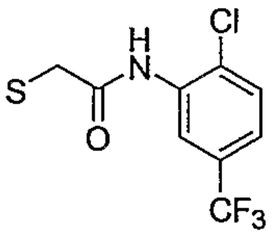
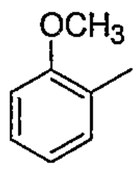
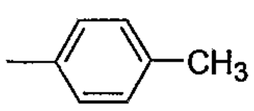
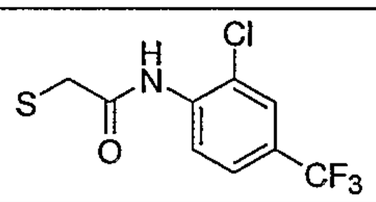
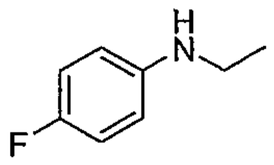
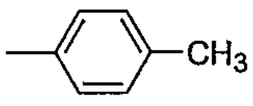
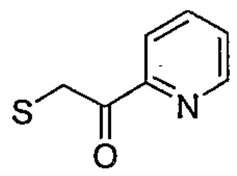
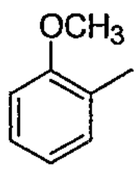
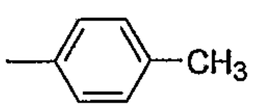
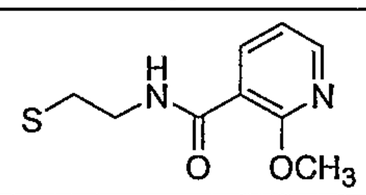
C14			
C15			
C16			
C17			
C18			
C19			
C20			
C21			
C22			
C23			
C24			
C25			
C26			
C27			

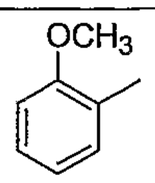
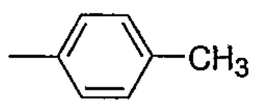
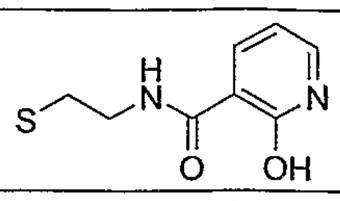
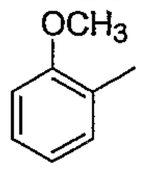
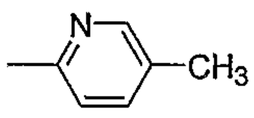
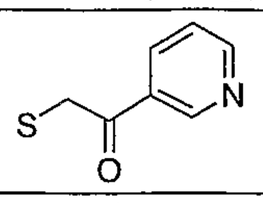
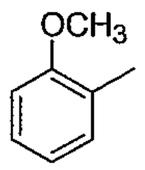
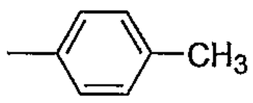
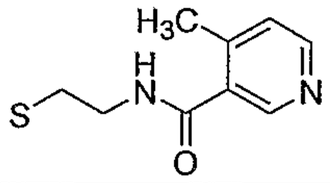
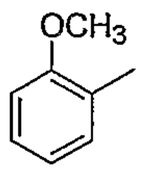
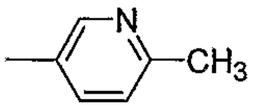
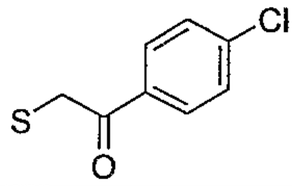
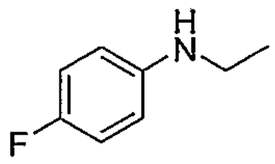
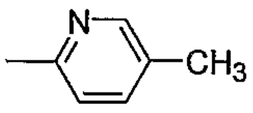
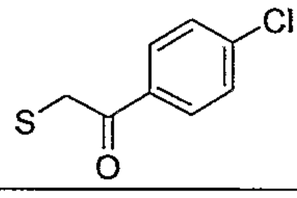
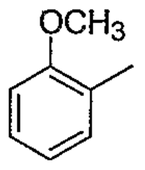
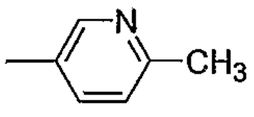
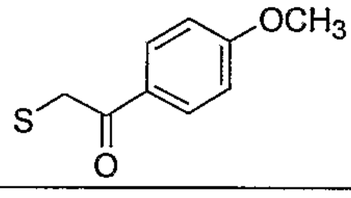
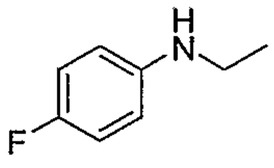
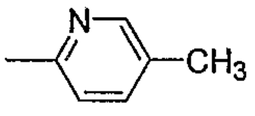
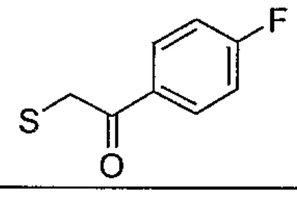
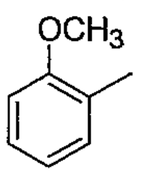
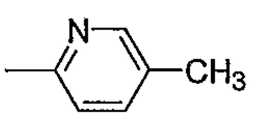
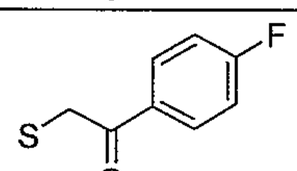
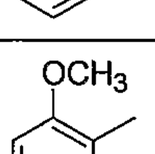
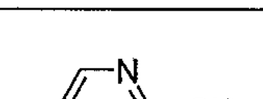
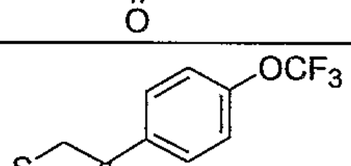
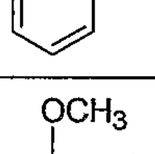
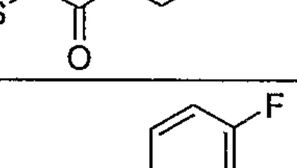
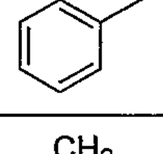
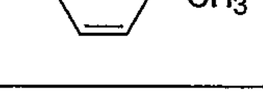
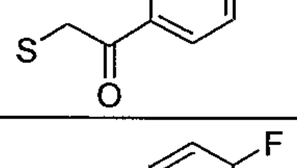
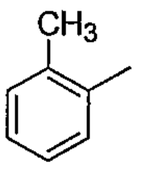
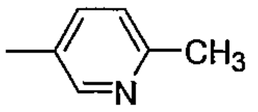
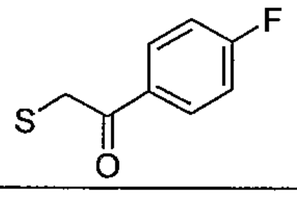
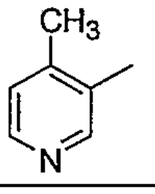
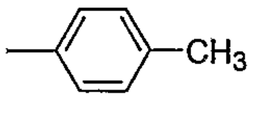
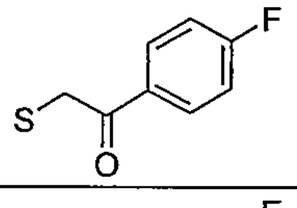
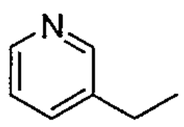
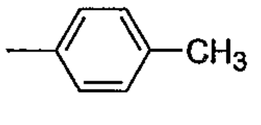
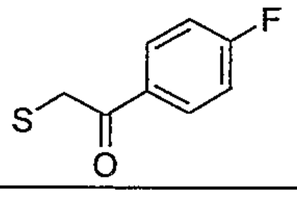
C28			
C29			
C30		CH_3	
C31			
C32			
C33			
C34			
C35			
C36			
C37			
C38			
C39			
C40		CH_3	
C41			
C42			
C43			

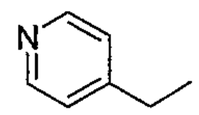
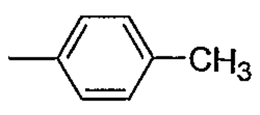
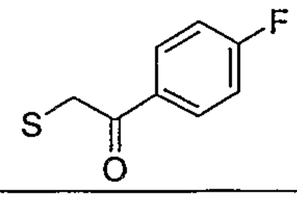
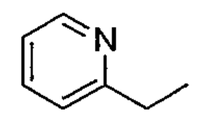
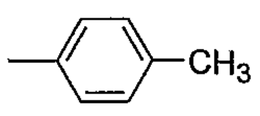
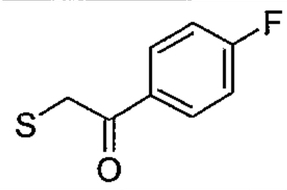
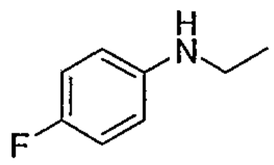
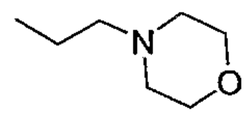
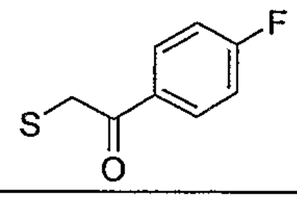
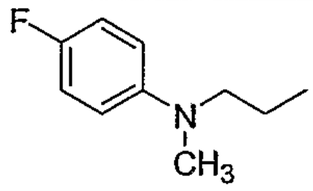
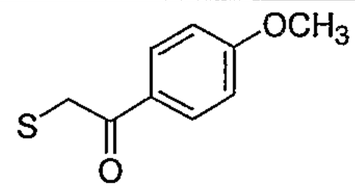
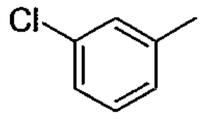
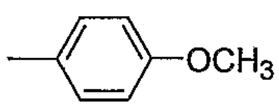
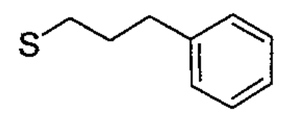
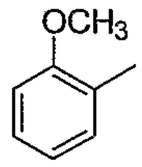
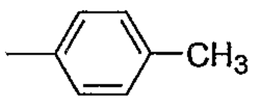
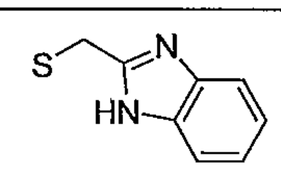
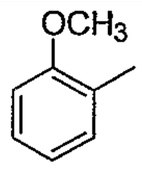
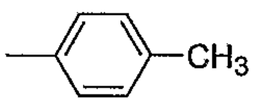
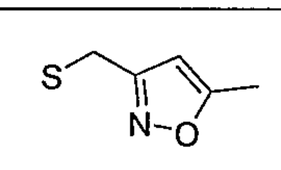
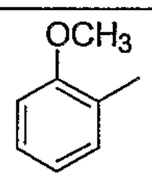
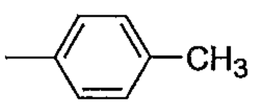
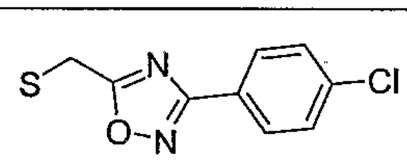
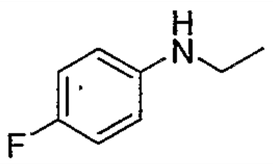
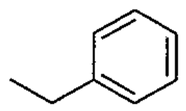
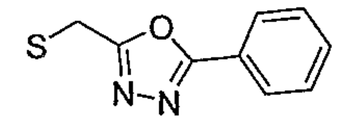
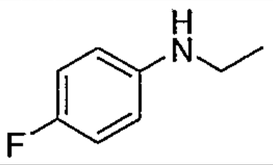
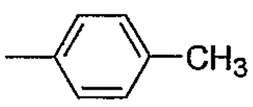
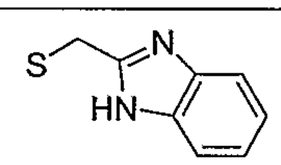
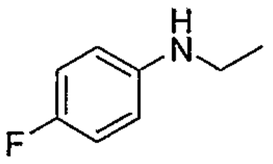
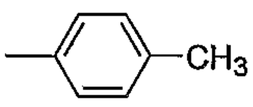
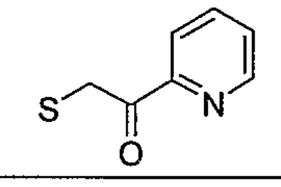
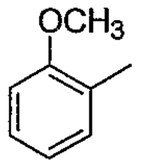
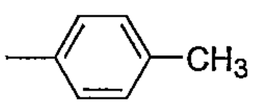
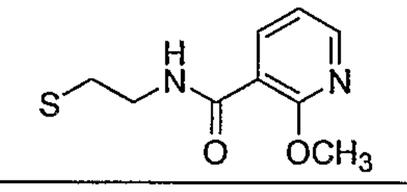
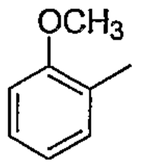
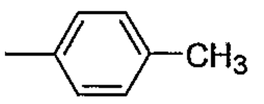
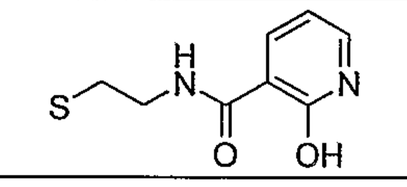
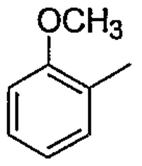
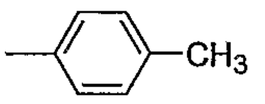
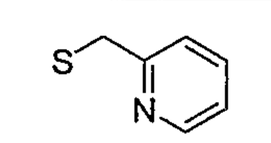
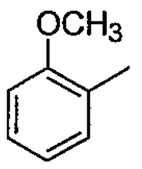
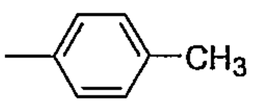
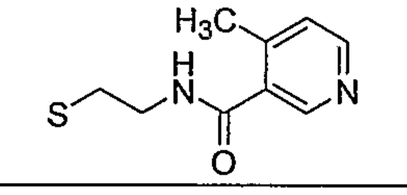
C44			
C45			
C46			
C47			
C48			
C49			
C50			
C51			
C52			
C53			
C54			
C55			
C56			
C57			

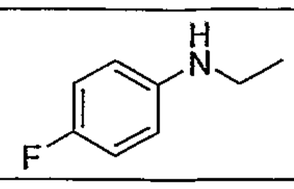
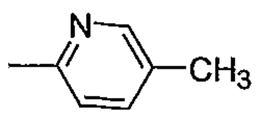
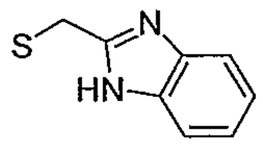
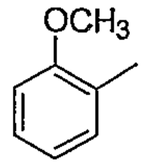
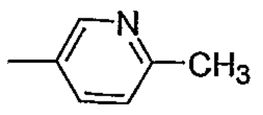
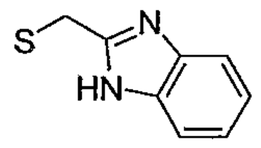
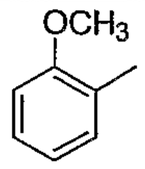
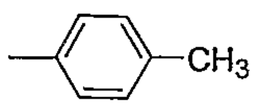
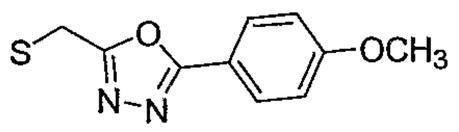
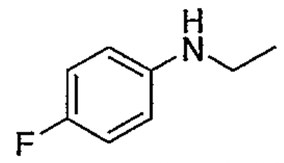
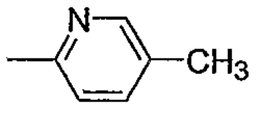
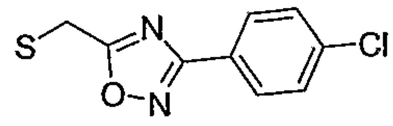
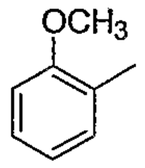
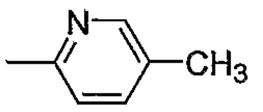
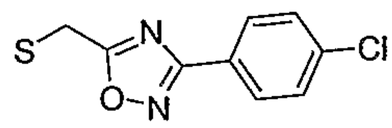
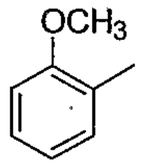
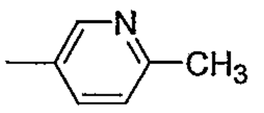
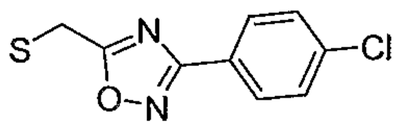
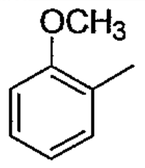
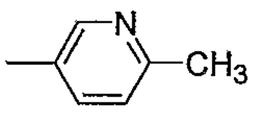
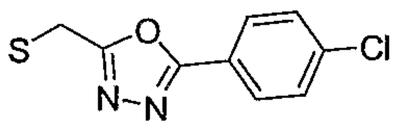
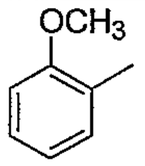
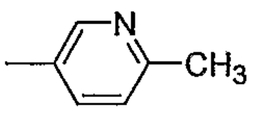
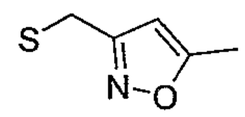
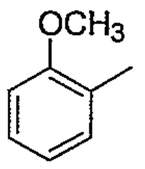
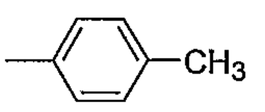
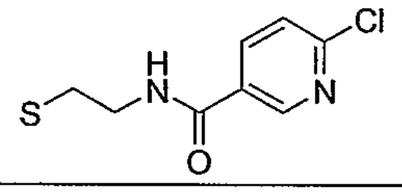
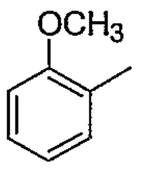
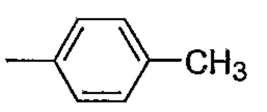
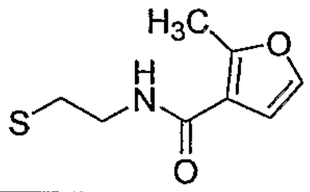
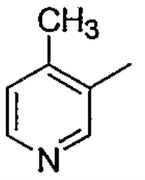
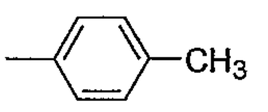
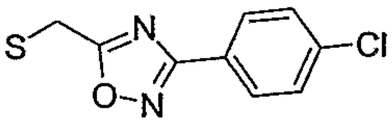
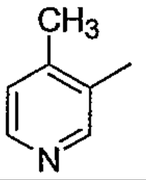
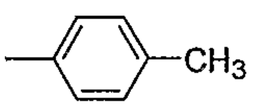
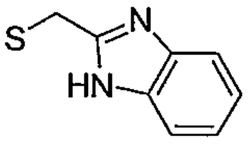
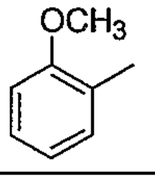
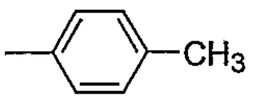
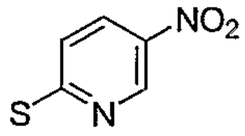
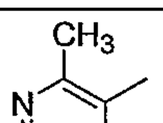
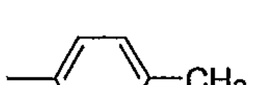
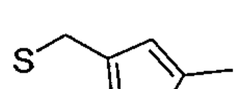
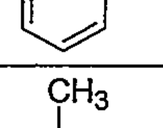
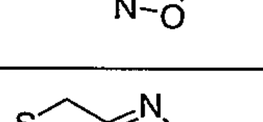
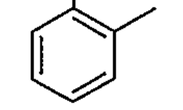
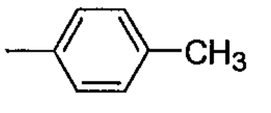
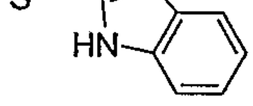
C58			
C59			
C60			
C61			
C62			
C63			
C64			
C65			
C66			
C67			
C68			
C69			
C70			
C71			

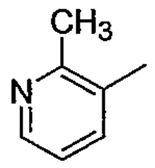
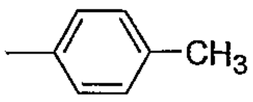
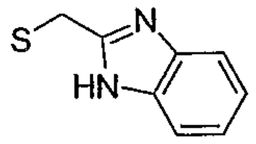
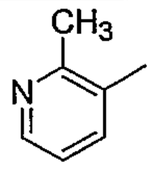
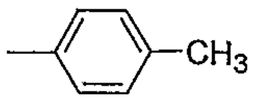
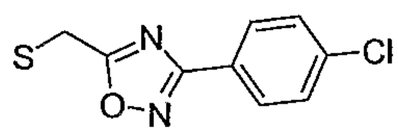
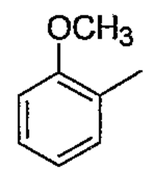
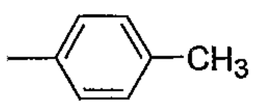
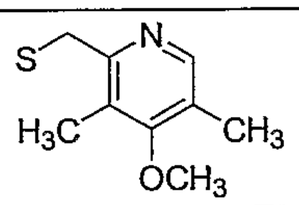
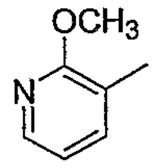
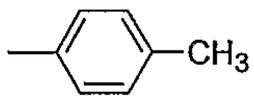
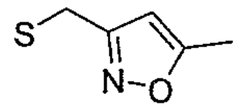
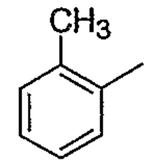
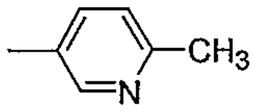
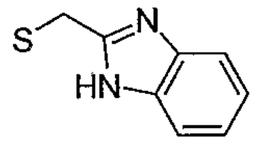
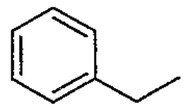
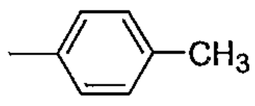
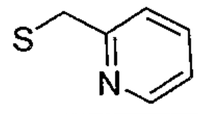
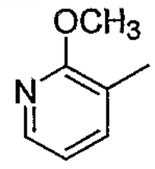
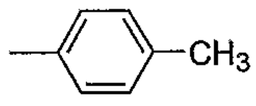
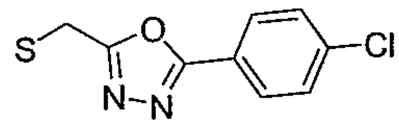
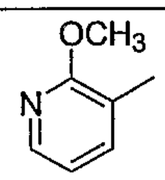
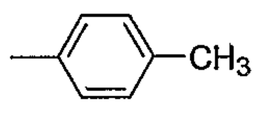
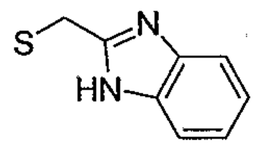
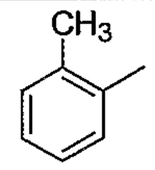
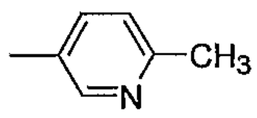
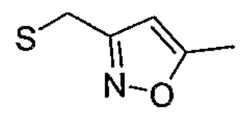
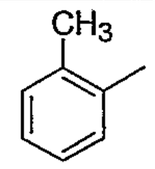
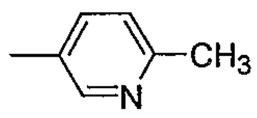
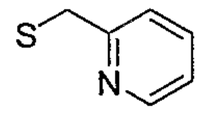
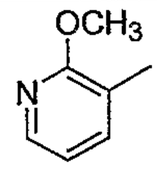
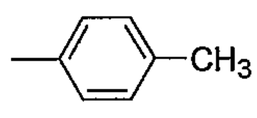
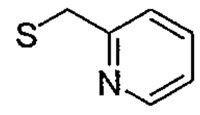
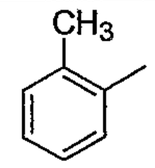
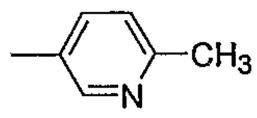
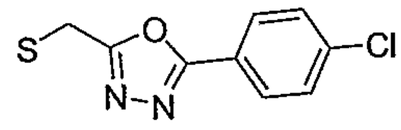
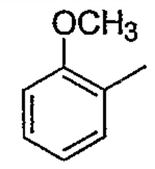
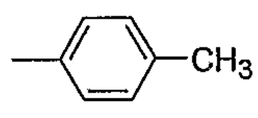
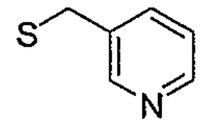
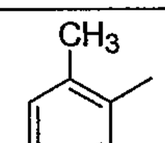
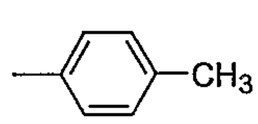
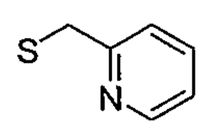
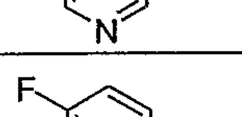
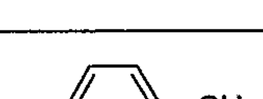
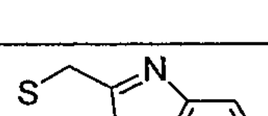
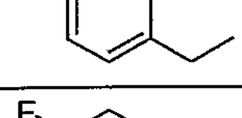
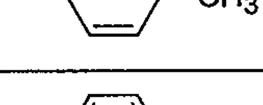
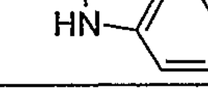
C72			
C73			
C74			
C75			
C76			
C77			
C78			
C79			
C80			
C81			
C82			
C83			
C84			
C85			
C86			

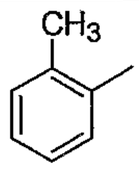
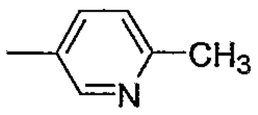
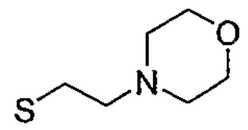
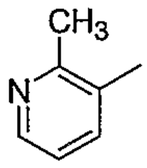
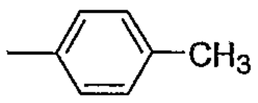
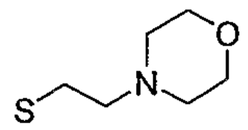
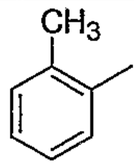
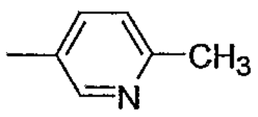
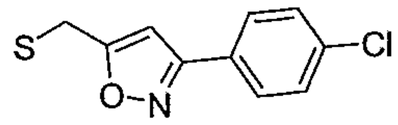
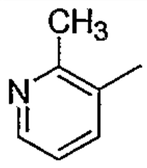
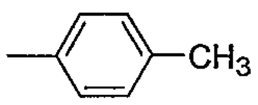
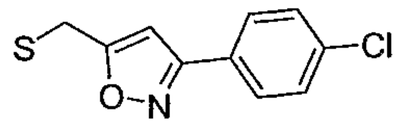
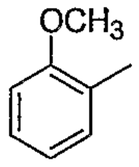
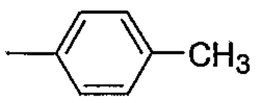
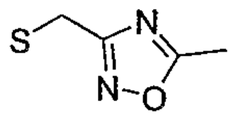
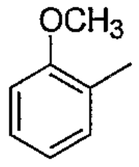
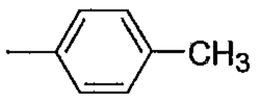
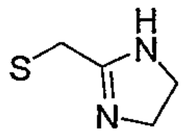
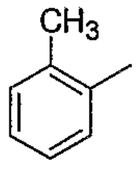
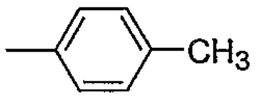
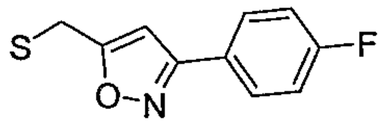
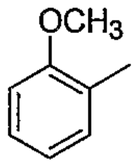
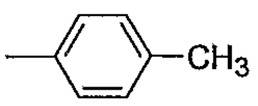
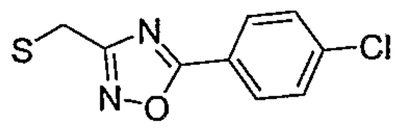
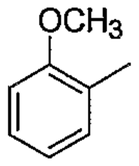
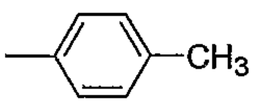
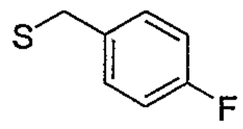
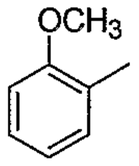
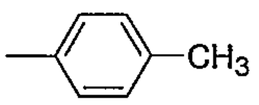
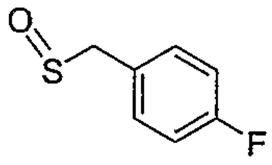
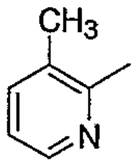
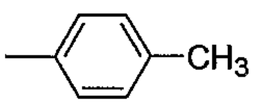
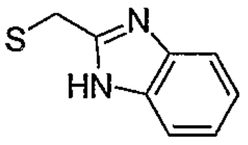
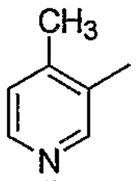
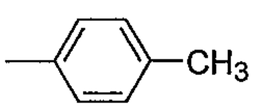
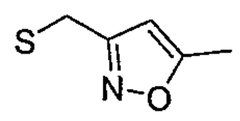
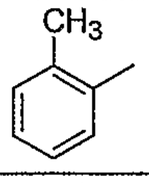
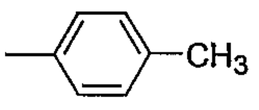
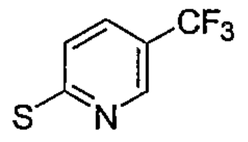
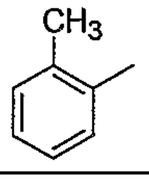
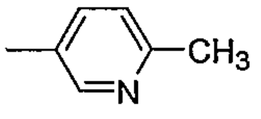
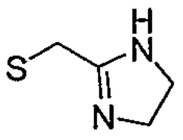
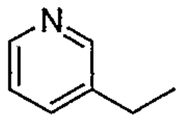
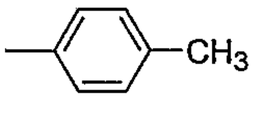
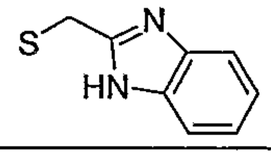
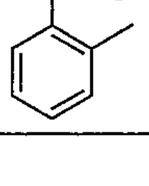
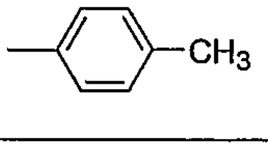
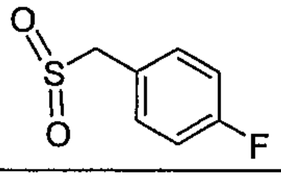
C87			
C88			
C89			
C90			
C91			
C92			
C93			
C94			
C95			
C96			
C97			
C98			
C99			
C100			
C101			

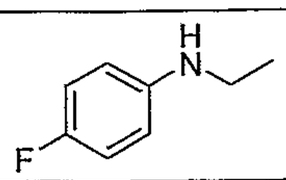
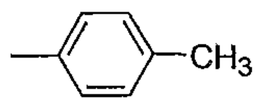
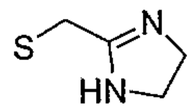
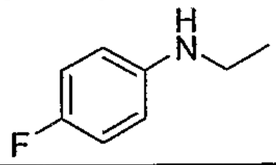
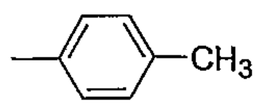
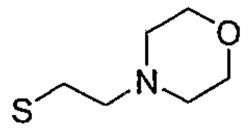
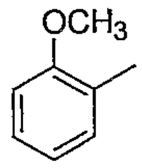
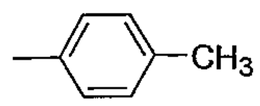
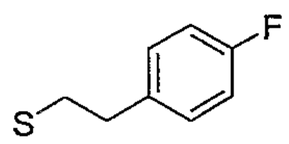
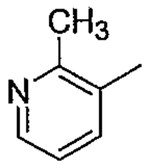
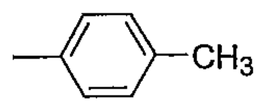
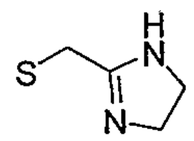
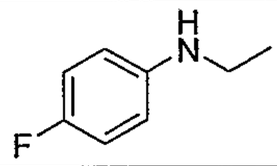
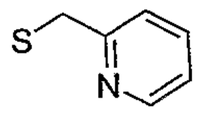
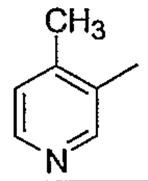
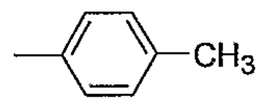
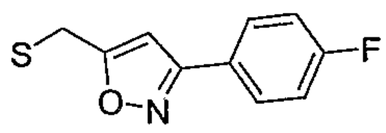
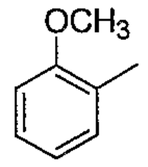
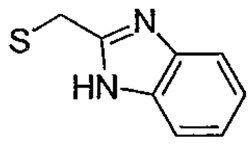
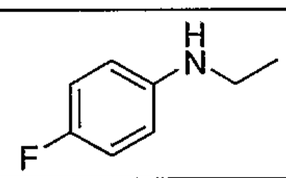
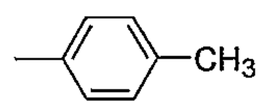
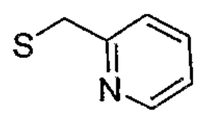
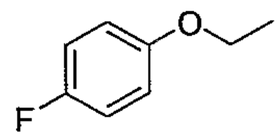
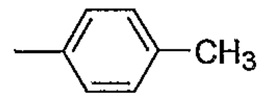
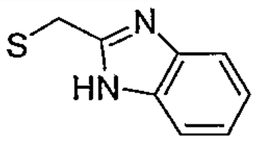
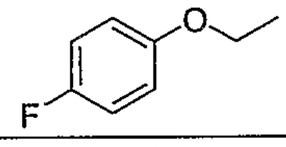
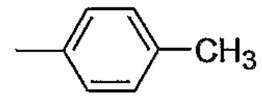
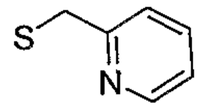
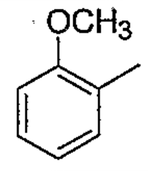
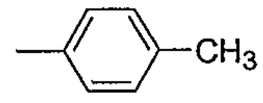
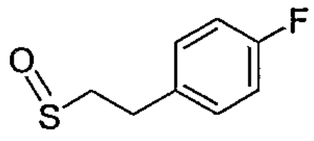
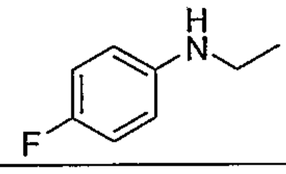
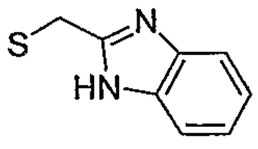
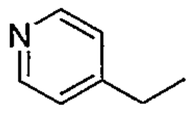
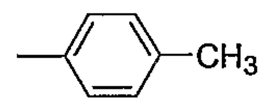
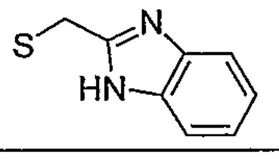
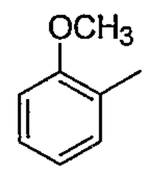
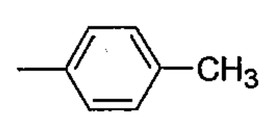
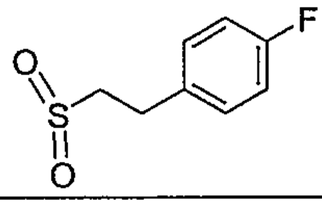
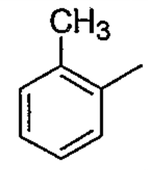
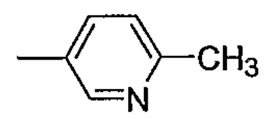
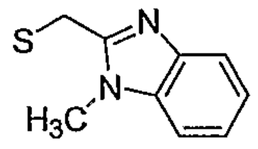
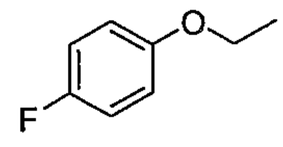
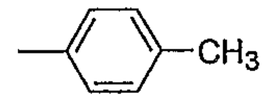
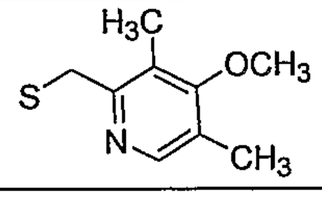
C102			
C103			
C104			
C105			
C106			
C107			
C108			
C109			
C110			
C111			
C112			
C113			
C114			
C115			

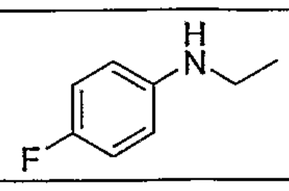
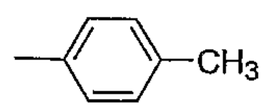
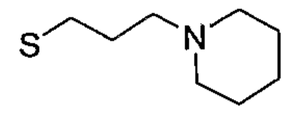
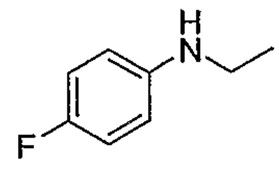
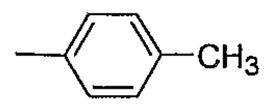
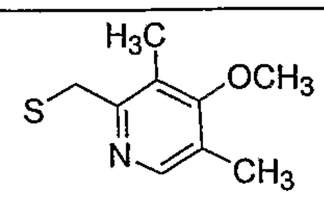
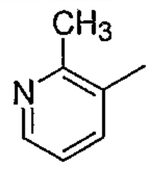
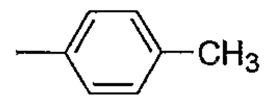
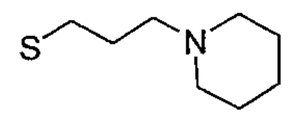
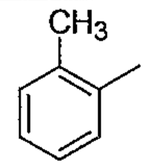
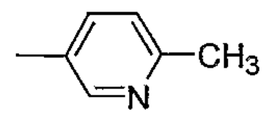
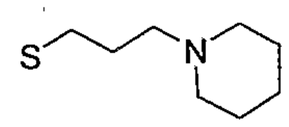
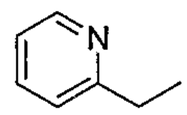
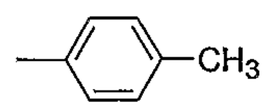
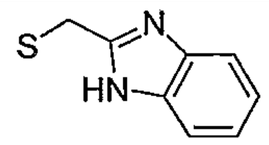
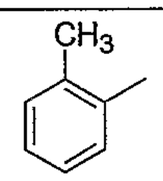
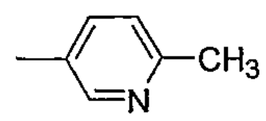
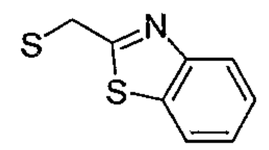
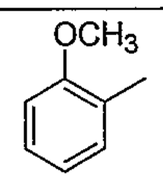
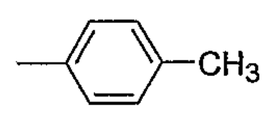
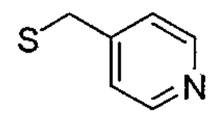
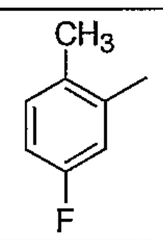
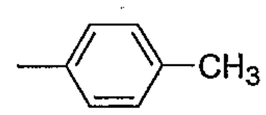
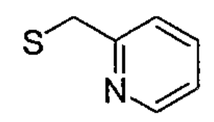
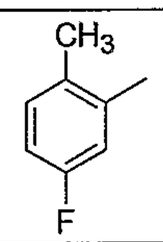
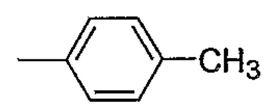
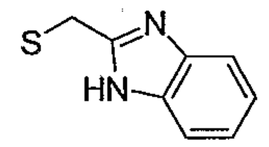
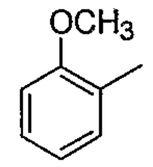
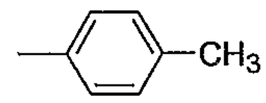
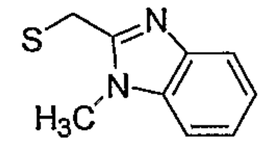
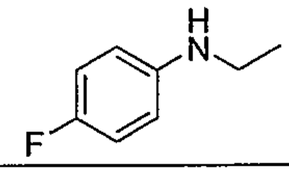
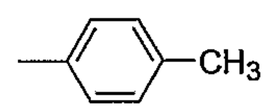
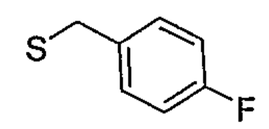
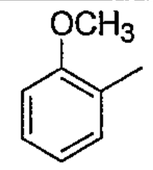
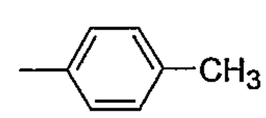
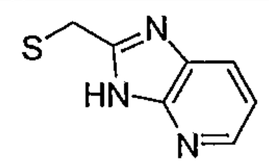
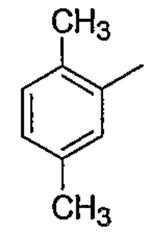
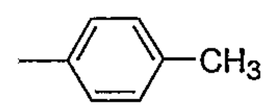
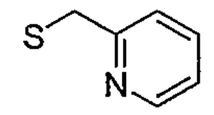
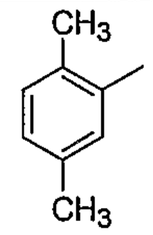
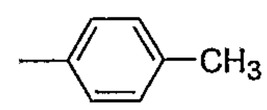
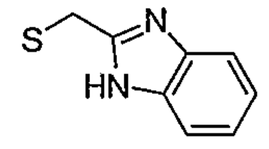
C116			
C117			
C118			
C119		CH_3	
C120			
C121			
C122			
C123			
C124			
C125			
C126			
C127			
C128			
C129			
C130			

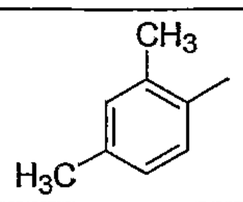
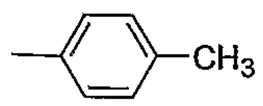
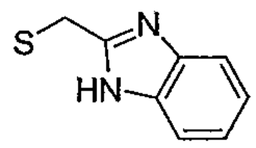
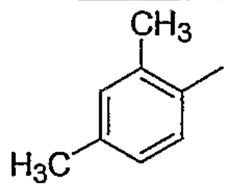
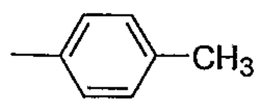
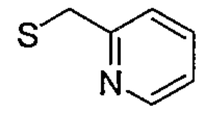
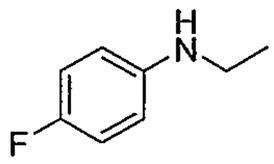
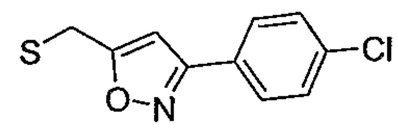
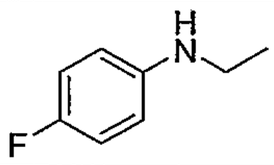
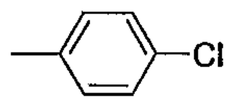
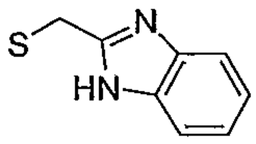
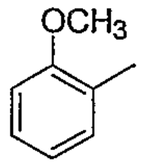
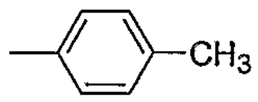
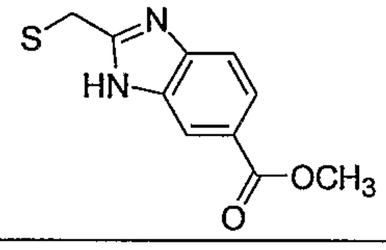
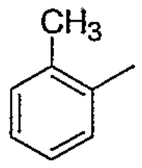
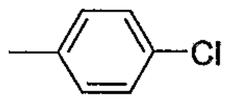
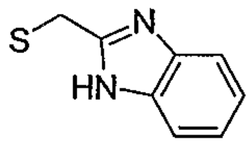
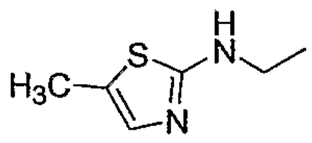
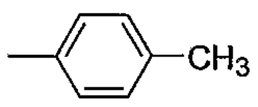
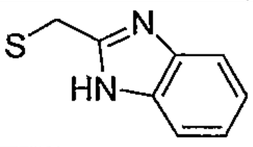
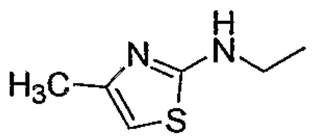
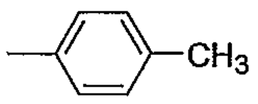
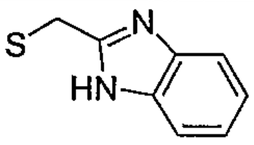
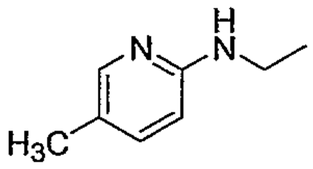
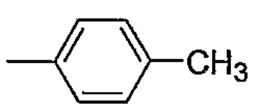
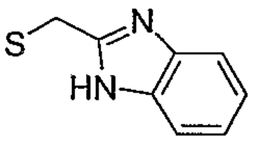
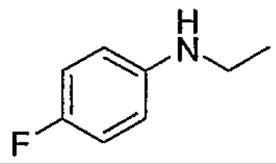
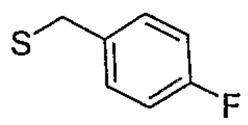
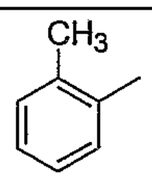
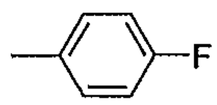
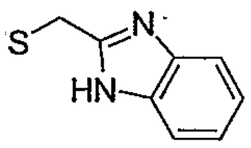
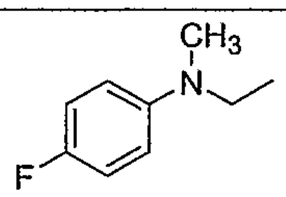
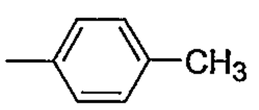
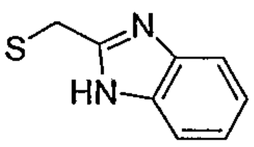
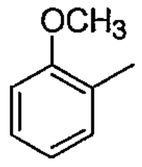
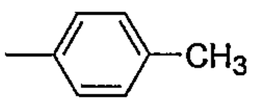
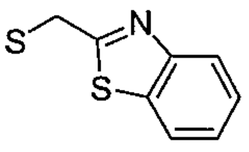
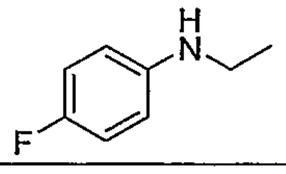
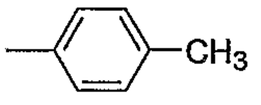
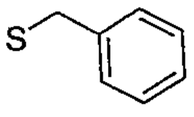
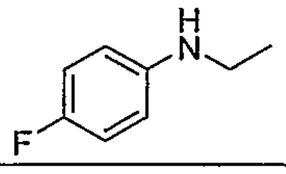
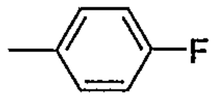
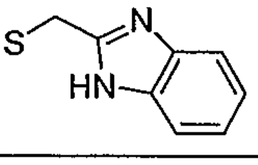
C131			
C132			
C133			
C134			
C135			
C136			
C137			
C138			
C139			
C140			
C141			
C142			
C143			
C144			
C145			
C146			

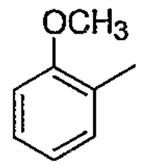
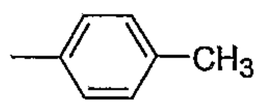
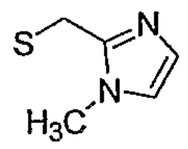
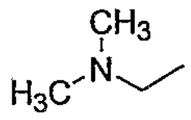
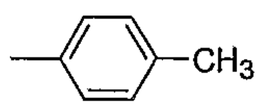
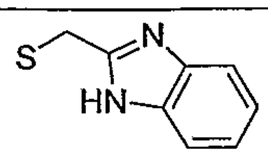
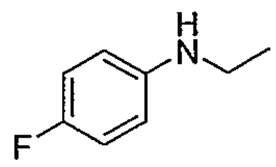
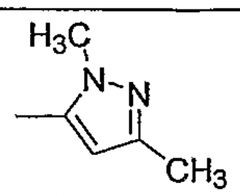
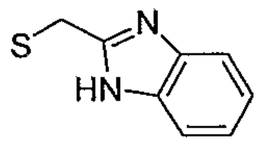
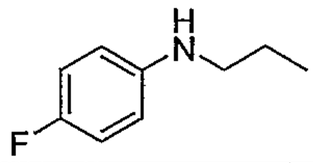
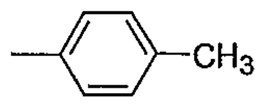
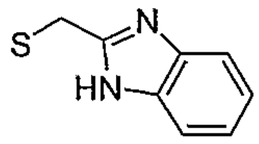
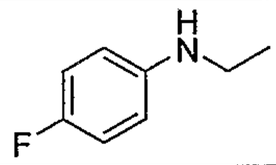
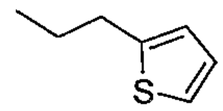
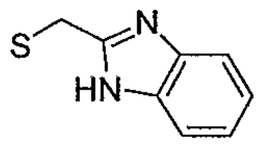
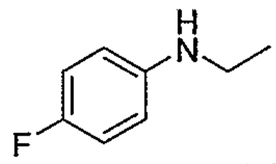
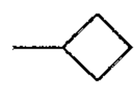
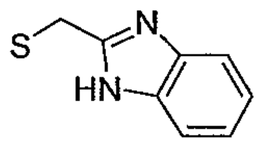
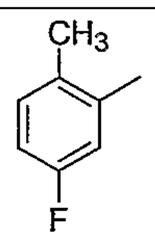
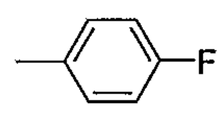
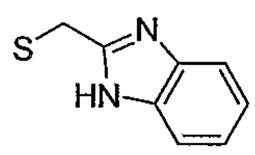
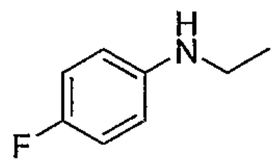
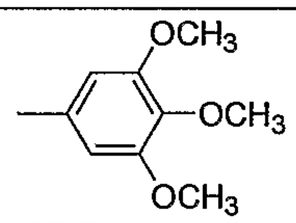
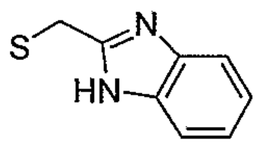
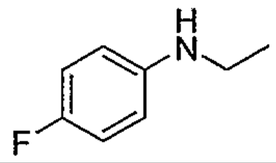
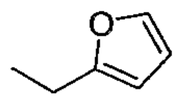
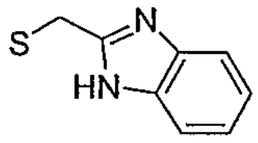
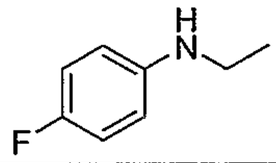
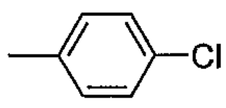
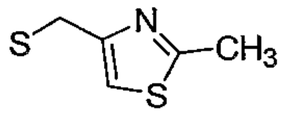
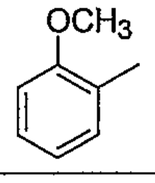
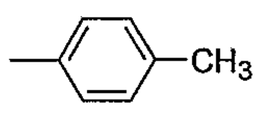
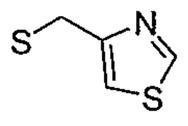
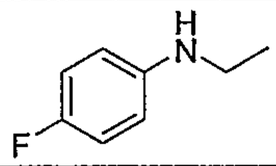
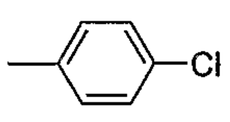
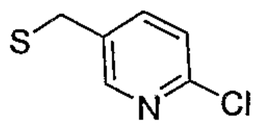
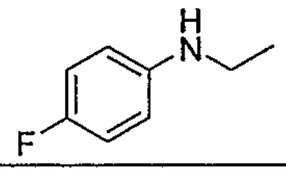
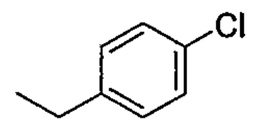
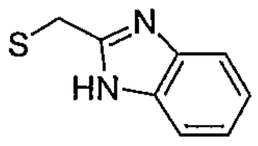
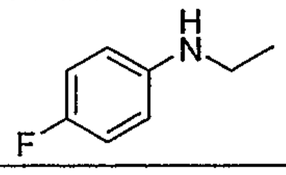
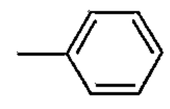
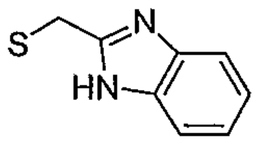
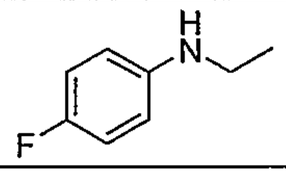
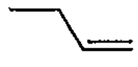
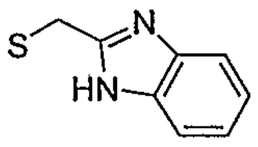
C147			
C148			
C149			
C150			
C151			
C152			
C153			
C154			
C155			
C156			
C157			
C158			
C159			
C160			
C161			
C162			

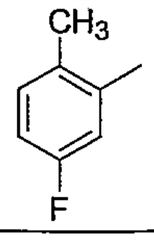
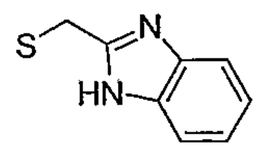
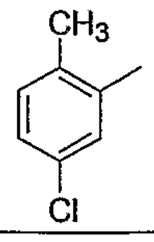
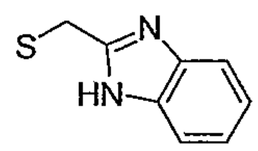
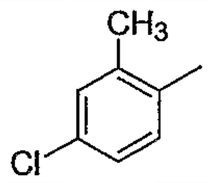
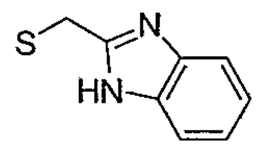
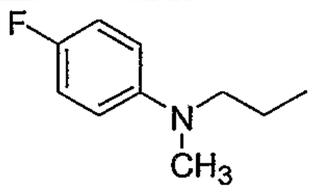
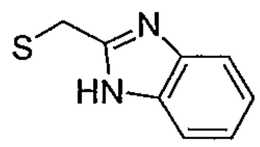
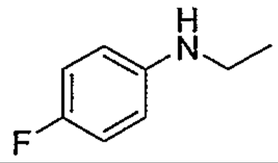
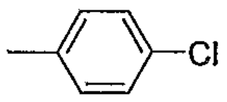
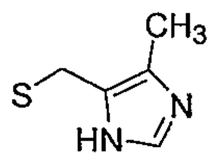
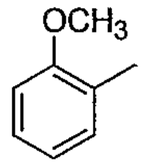
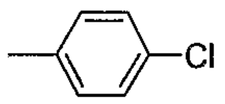
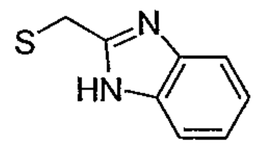
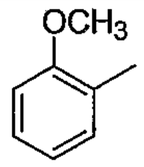
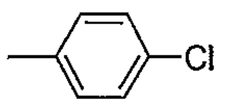
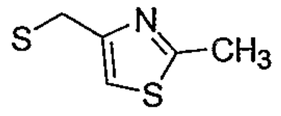
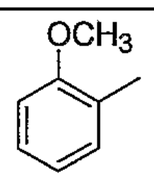
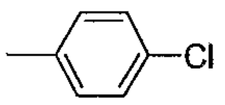
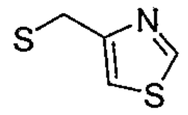
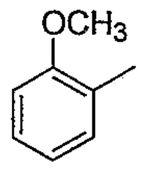
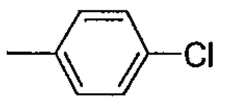
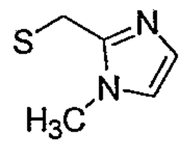
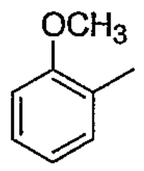
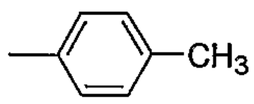
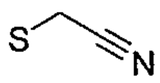
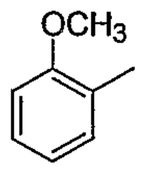
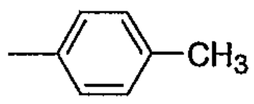
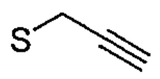
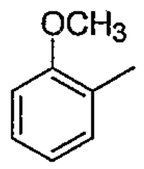
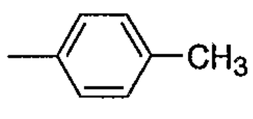
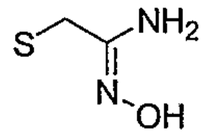
C163			
C164			
C165			
C166			
C167			
C168			
C169			
C170			
C171			
C172			
C173			
C174			
C175			
C176			
C177			
C178			

C179			
C180			
C181			
C182			
C183		CH_3	
C184			
C185		CH_3	
C186			
C187			
C188			
C189			
C190		CH_3	
C191			
C192			
C193			
C194			

C195			
C196			
C197			
C198			
C199			
C200			
C201			
C202			
C203			
C204			
C205			
C206			
C207			
C208			

C209			
C210			
C211		CH_3	
C212			
C213			
C214			
C215			
C216			
C217			
C218		CH_3	
C219			
C220			
C221			
C222			
C223			

C224			
C225			
C226			
C227			
C228			
C229			
C230			
C231			
C232			
C233			
C234			
C235			
C236			
C237			
C238			

C239		CH3	
C240		CH3	
C241		CH3	
C242		CH_3	
C243			
C244			
C245			
C246			
C247			
C248			
C249			
C250			

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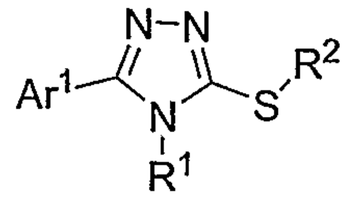

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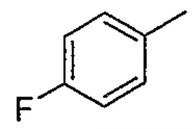
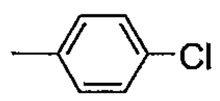
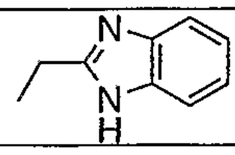
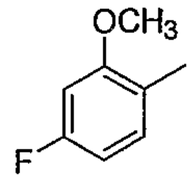
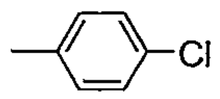
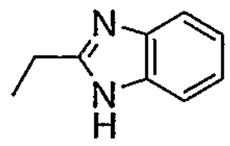
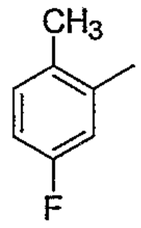
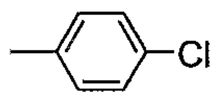
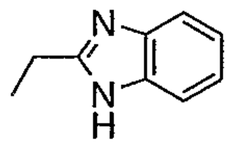
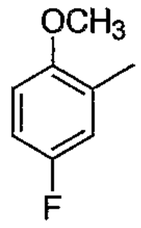
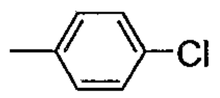
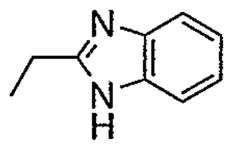
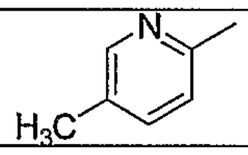
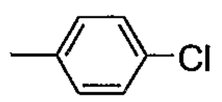
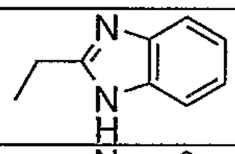
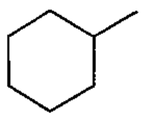
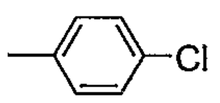
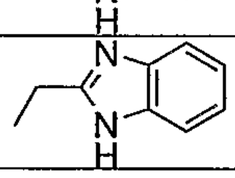
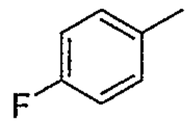
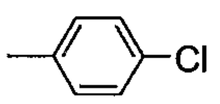
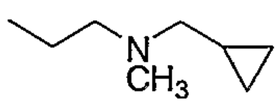
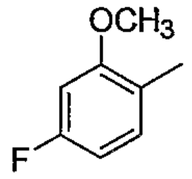
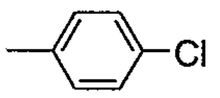
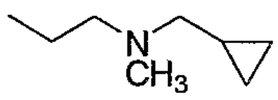
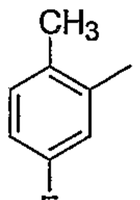
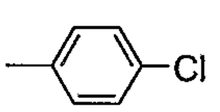
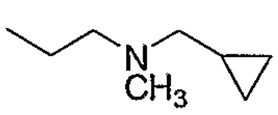
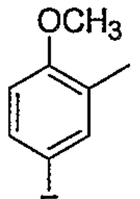
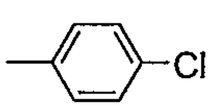
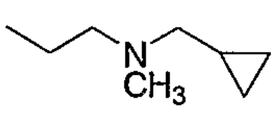
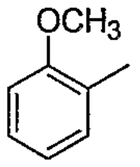
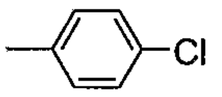
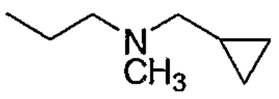
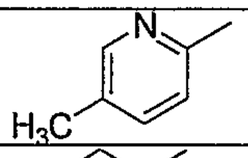
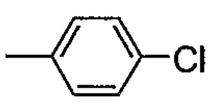
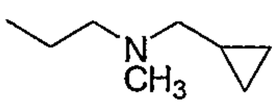
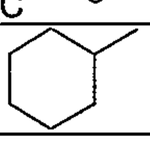
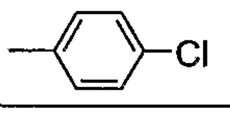
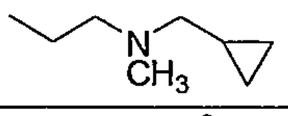
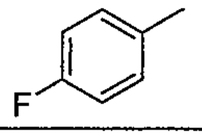
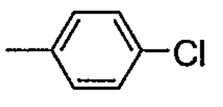
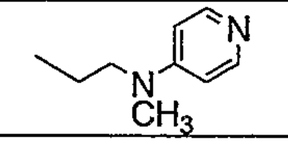
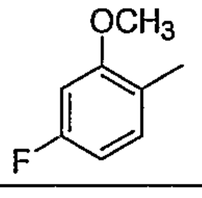
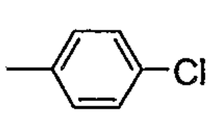
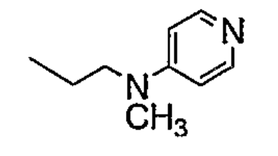
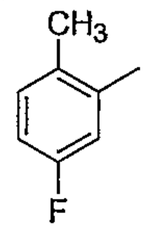
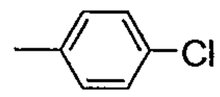
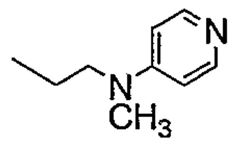
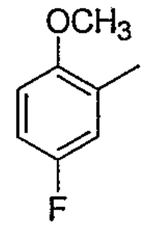
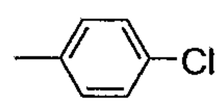
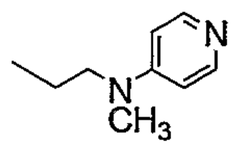
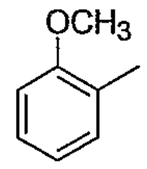
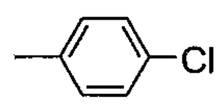
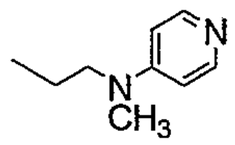
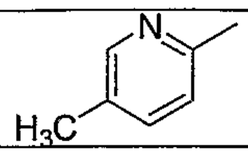
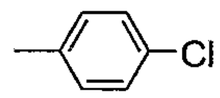
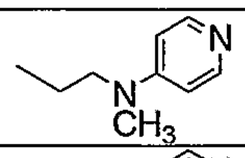
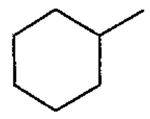
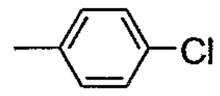
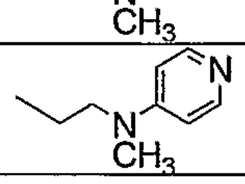
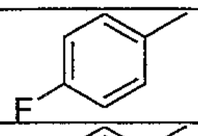
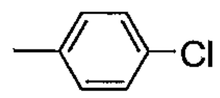
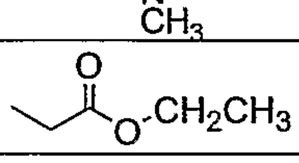
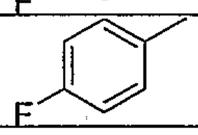
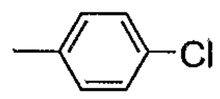
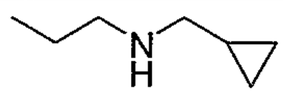
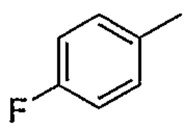
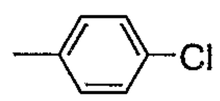
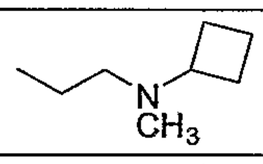
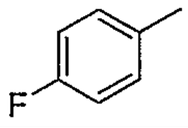
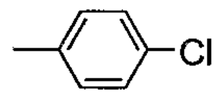
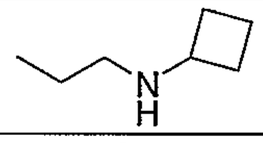
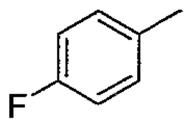
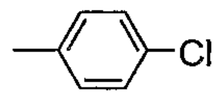
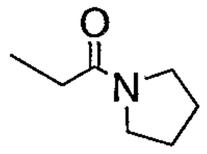
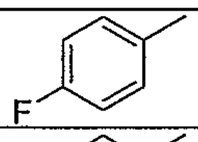
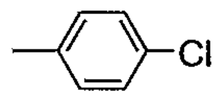
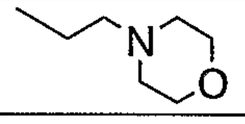
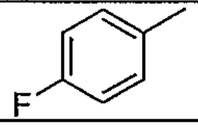
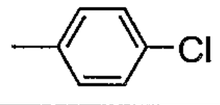
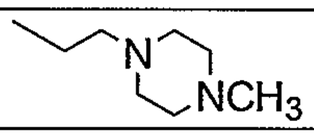
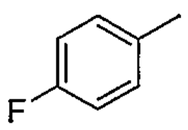
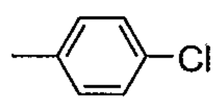
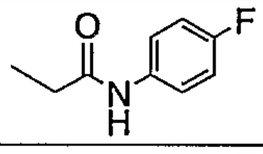
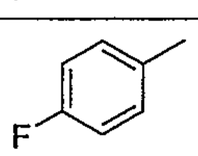
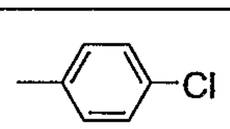
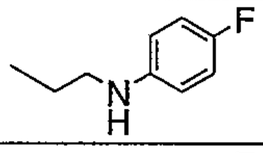
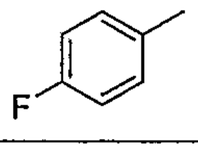
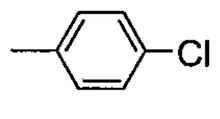
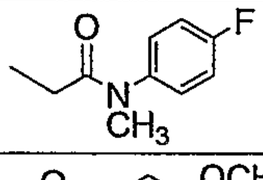
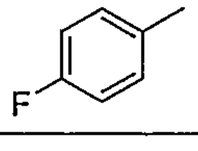
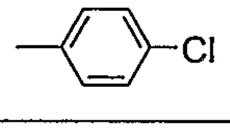
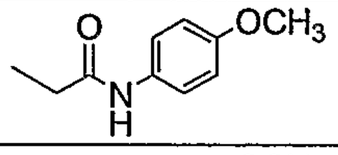
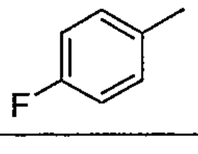
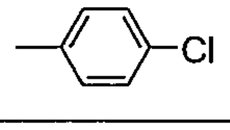
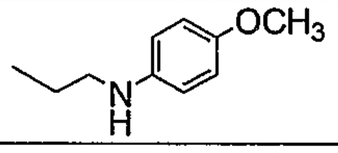
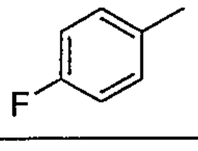
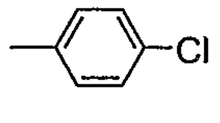
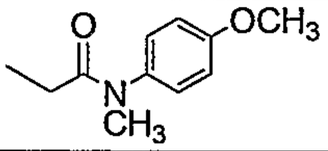
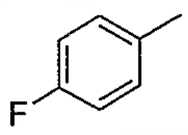
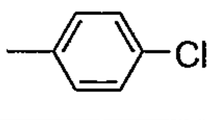
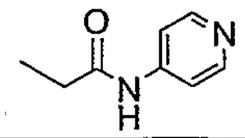
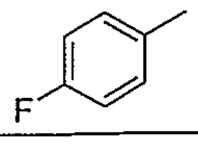
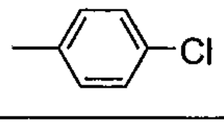
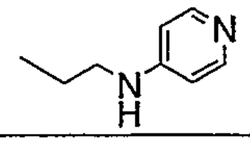
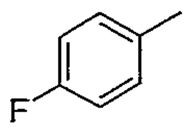
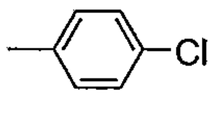
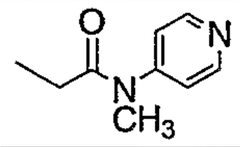
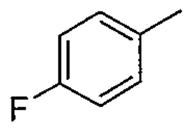
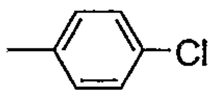
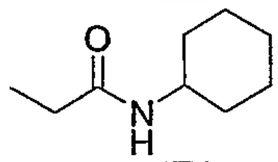
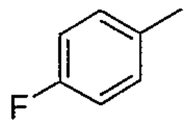
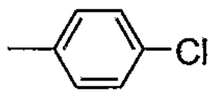
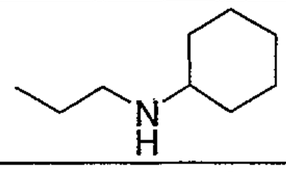
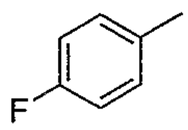
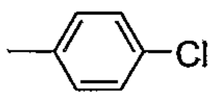
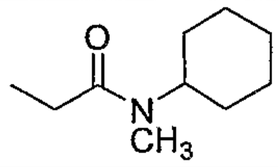
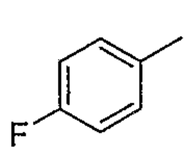
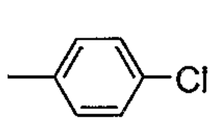
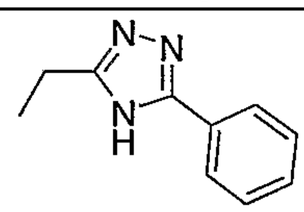
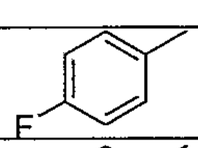
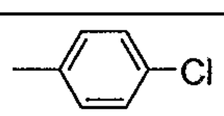
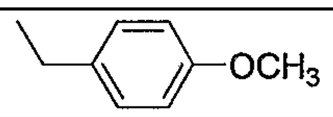
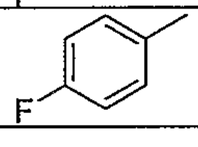
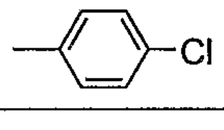
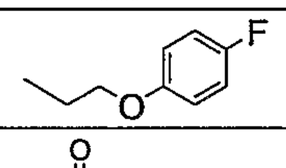
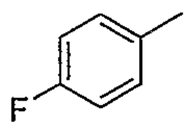
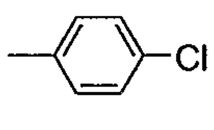
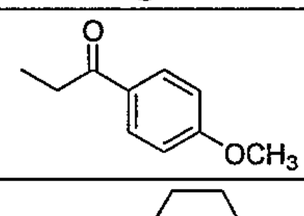
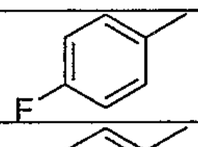
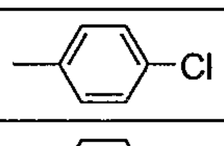
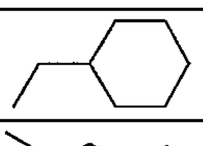
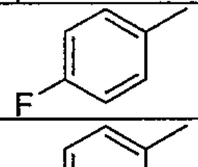
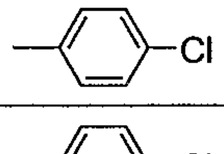
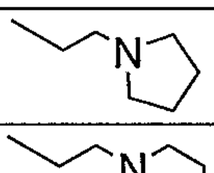
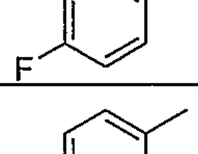
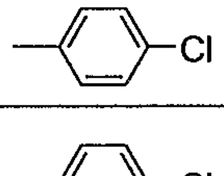
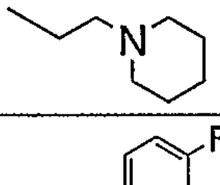
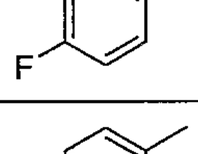
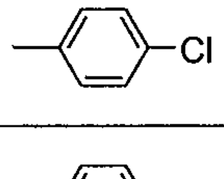
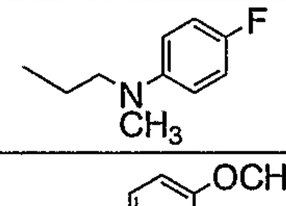
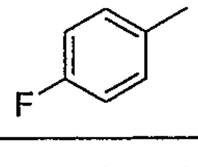
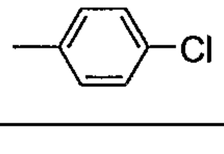
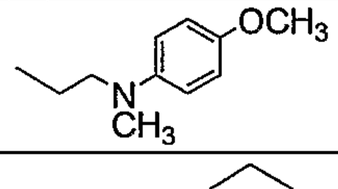
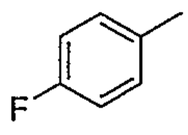
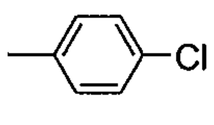
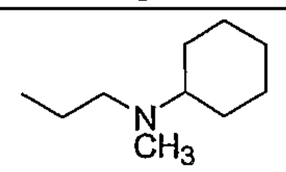
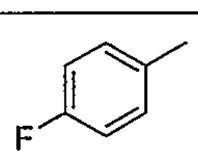
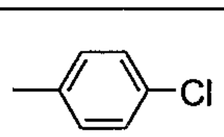
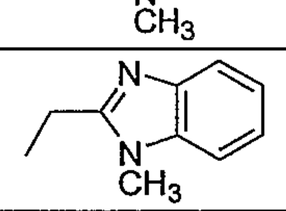
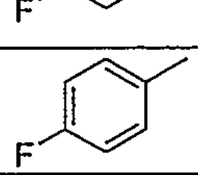
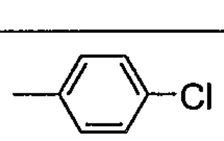
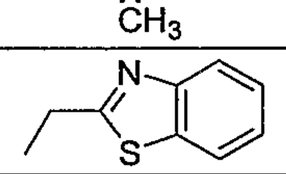
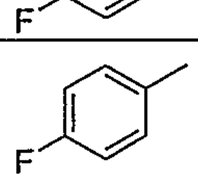
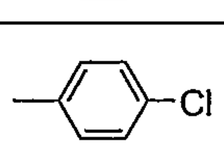
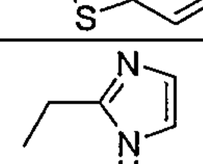
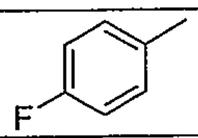
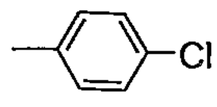
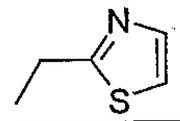
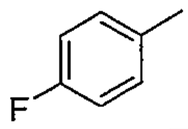
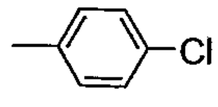
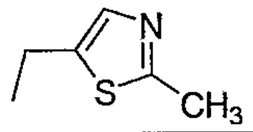
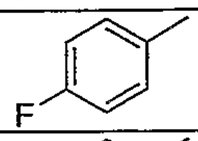
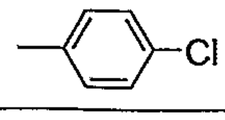
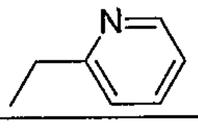
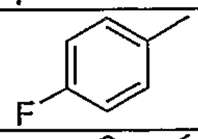
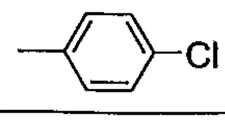
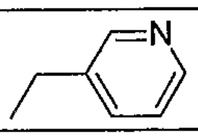
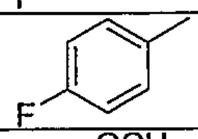
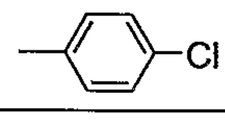
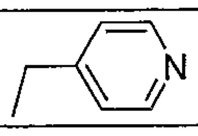
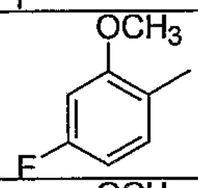
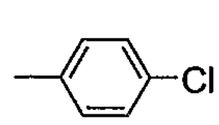
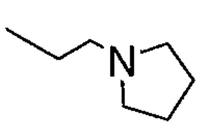
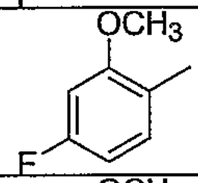
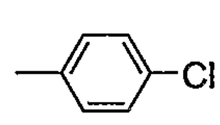
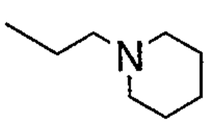
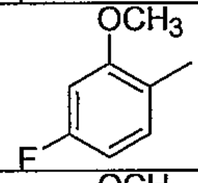
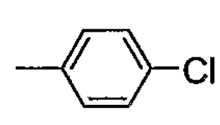
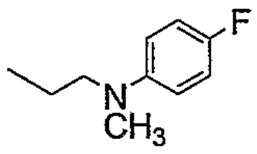
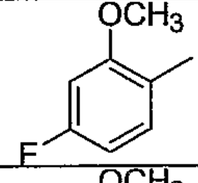
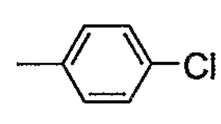
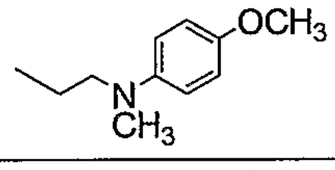
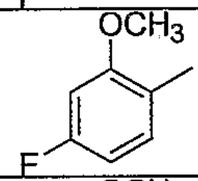
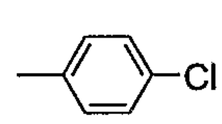
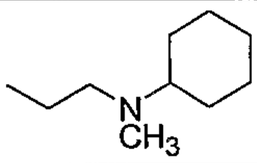
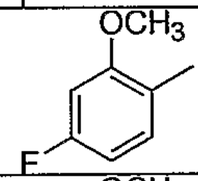
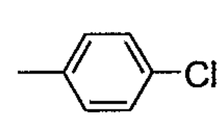
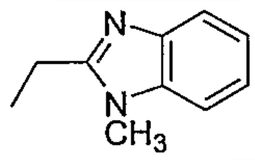
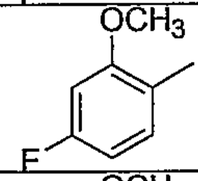
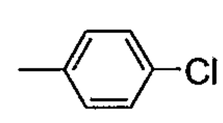
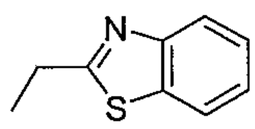
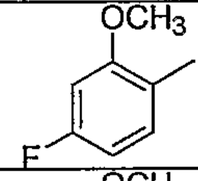
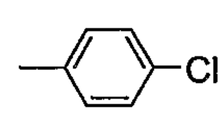
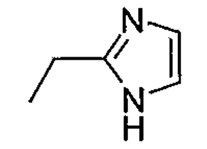
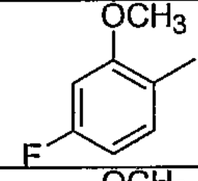
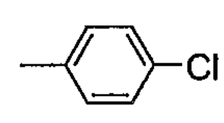
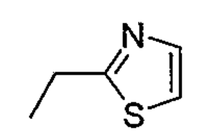
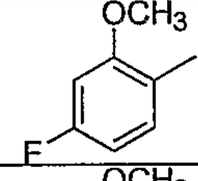
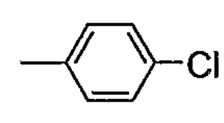
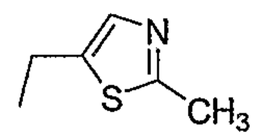
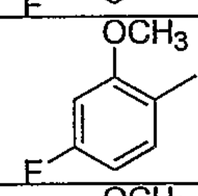
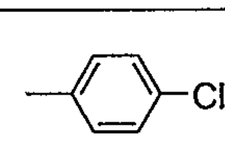
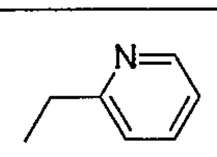
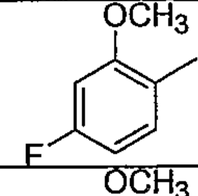
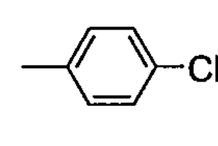
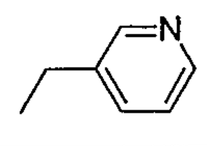
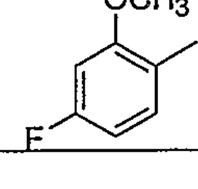
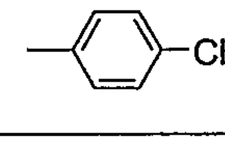
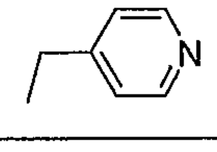
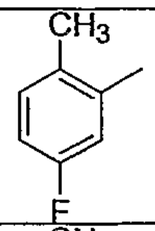
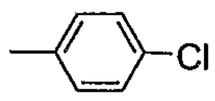
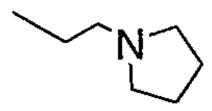
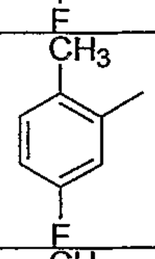
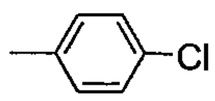
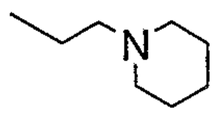
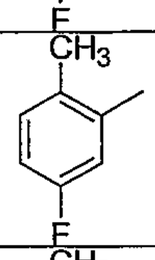
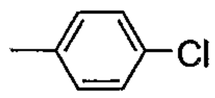
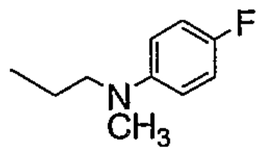
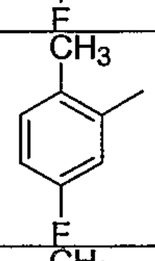
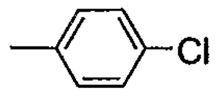
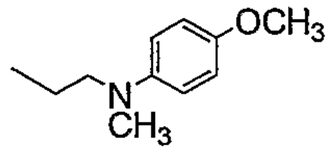
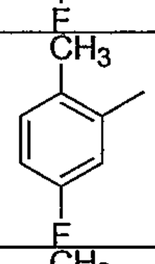
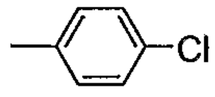
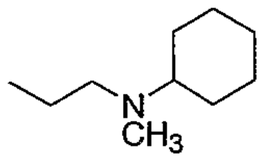
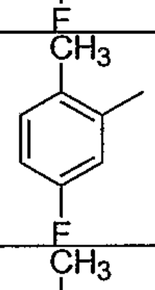
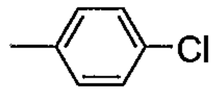
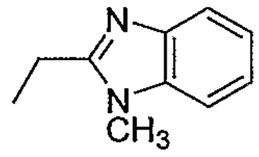
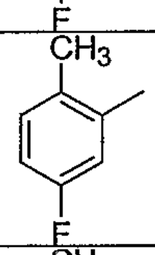
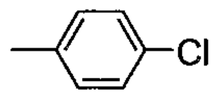
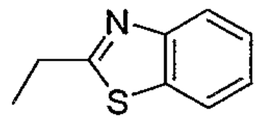
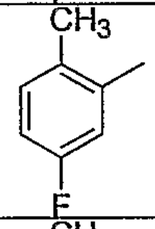
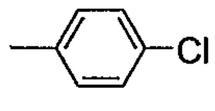
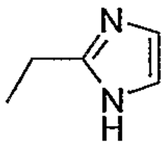
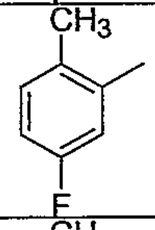
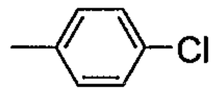
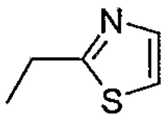
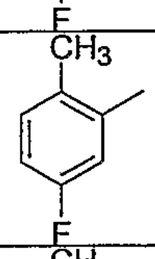
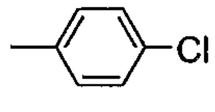
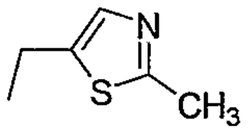
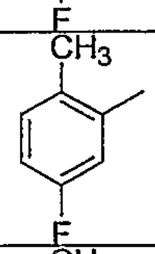
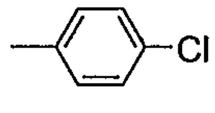
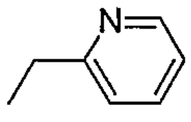
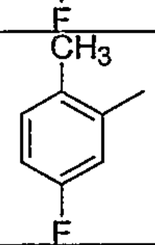
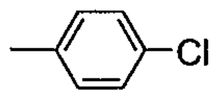
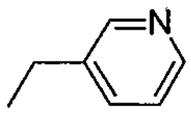
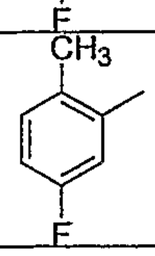
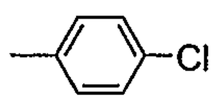
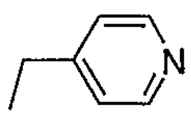
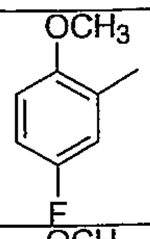
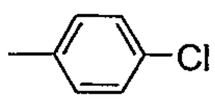
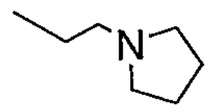
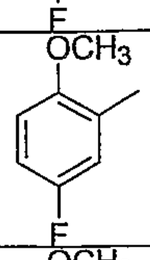
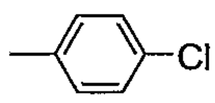
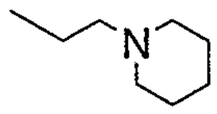
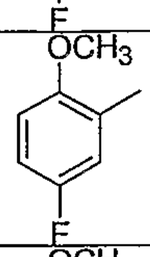
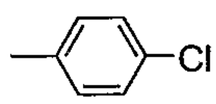
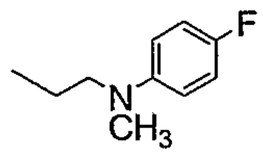
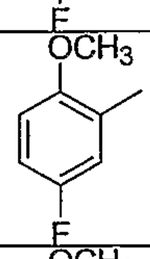
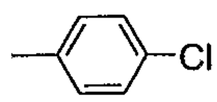
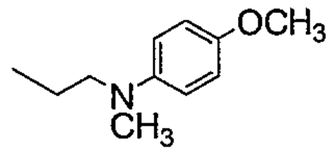
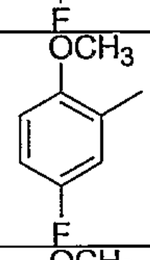
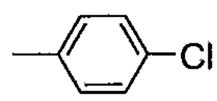
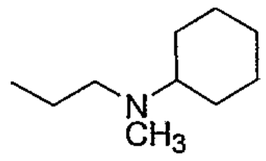
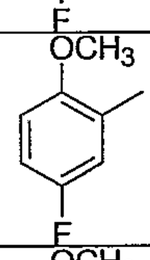
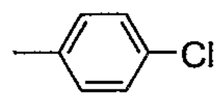
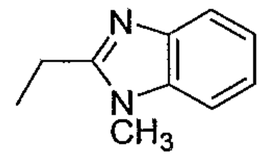
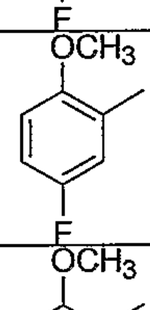
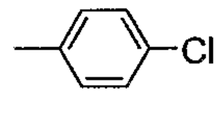
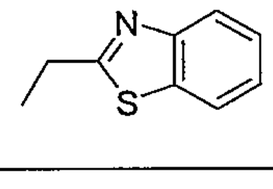
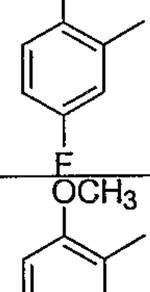
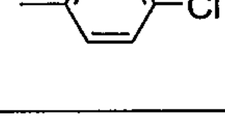
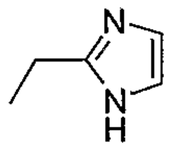
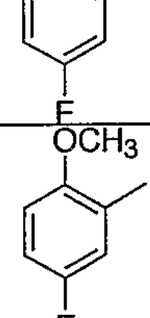
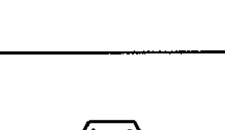
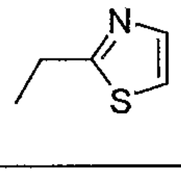
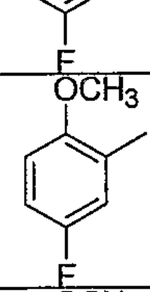
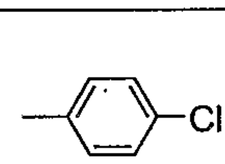
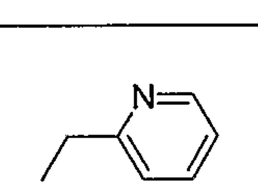
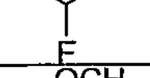
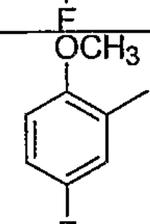
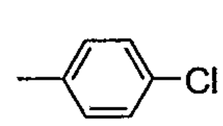
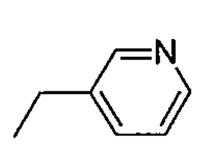
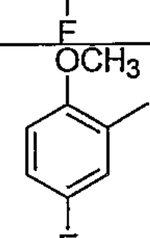
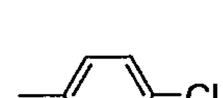
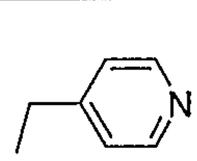
C251			
C252			
C253			
C254			
C255			
C256			
C257			
C258			
C259			
C260			
C261			
C262			
C263			
C264			
C265			

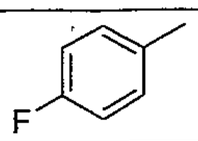
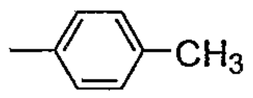
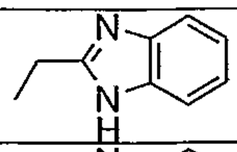
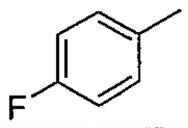
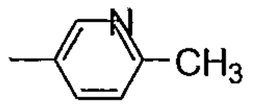
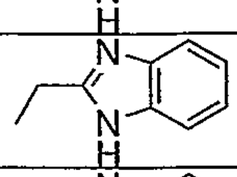
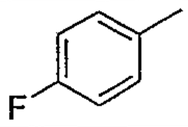
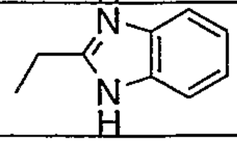
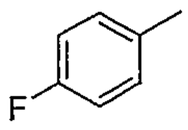
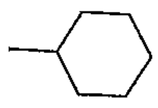
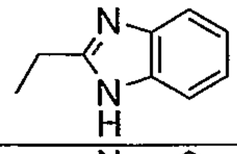
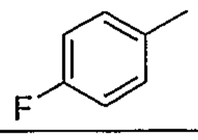
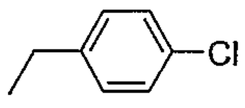
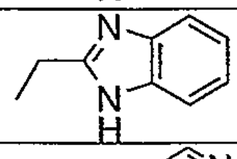
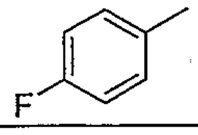
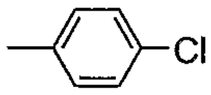
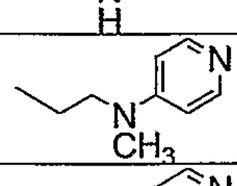
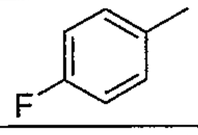
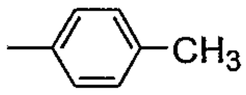
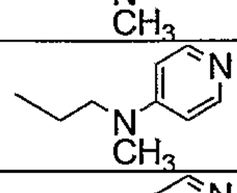
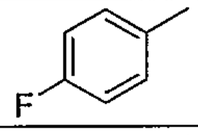
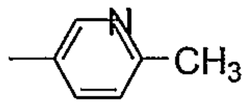
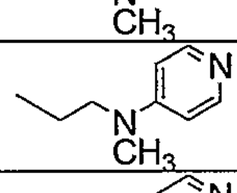
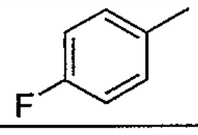
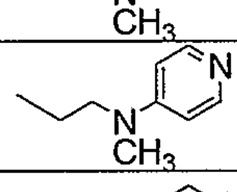
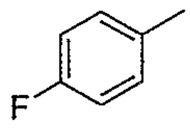
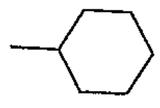
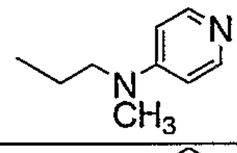
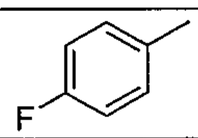
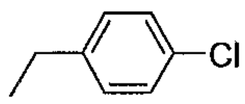
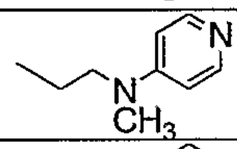
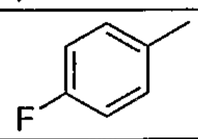
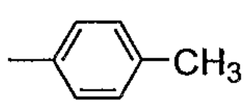
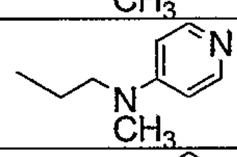
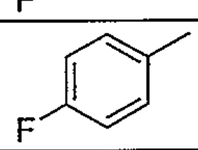
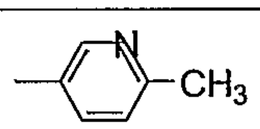
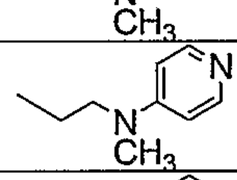
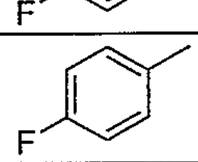
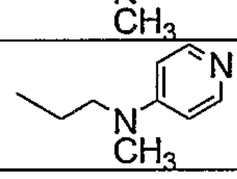
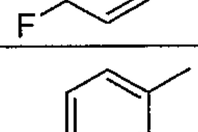
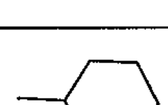
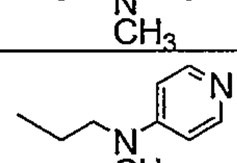
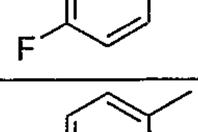
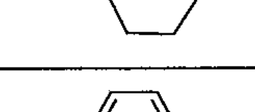
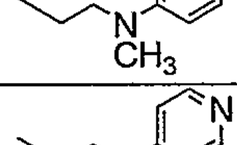
C266			
C267			
C268			
C269			
C270			
C271			
C272			
C273			
C274			
C275			
C276			
C277			
C278			
C279			
C280			
C281			
C282			
C283			

C284			
C285			
C286			
C287			
C288			
C289			
C290			
C291			
C292			
C293			
C294			
C295			
C296			
C297			
C298			
C299			
C300			
C301			
C302			

C303			
C304			
C305			
C306			
C307			
C308			
C309			
C310			
C311			
C312			
C313			
C314			
C315			
C316			
C317			
C318			
C319			
C320			

C321			
C322			
C323			
C324			
C325			
C326			
C327			
C328			
C329			
C330			
C331			
C332			
C333			

C334			
C335			
C336			
C337			
C338			
C339			
C340			
C341			
C342			
C343			
C344			
C345			
C346			

C347			
C348			
C349		CH_3	
C350			
C351			
C352			
C353			
C354			
C355		CH_3	
C356			
C357			
C358			
C359			
C360		CH_3	
C361			
C362			

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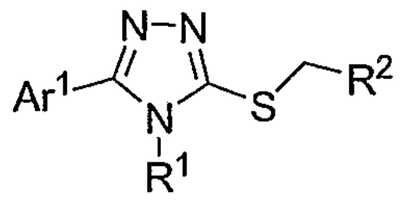
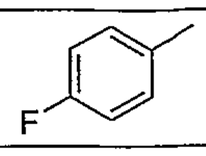
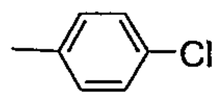
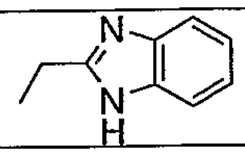
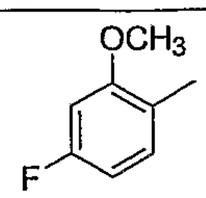
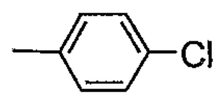
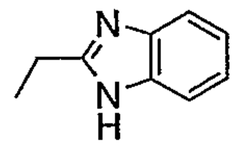
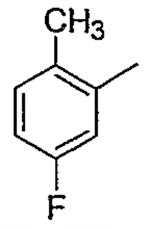
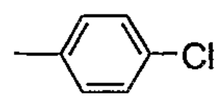
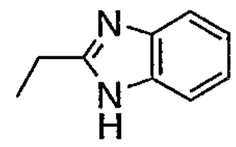
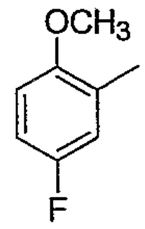
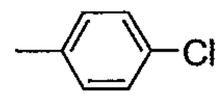
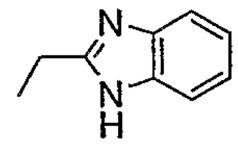
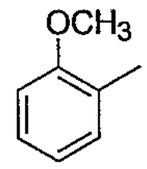
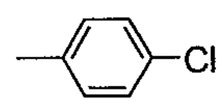
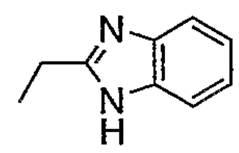
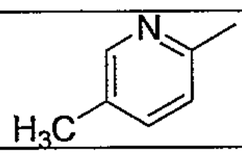
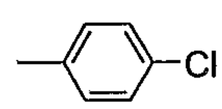
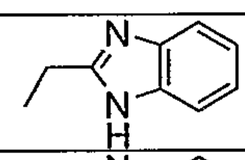
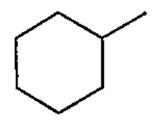
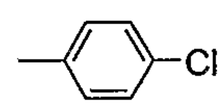
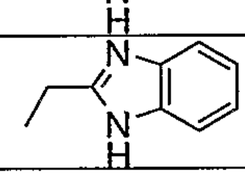
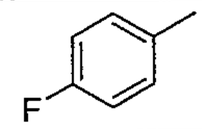
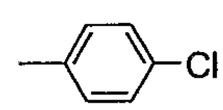
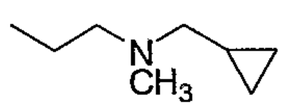
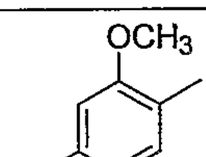
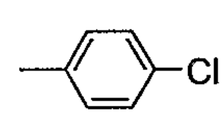
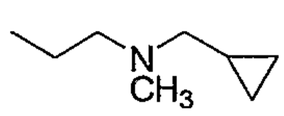
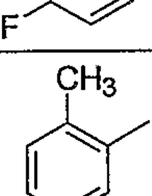
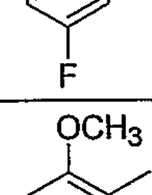
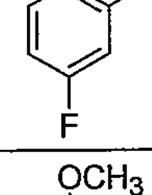
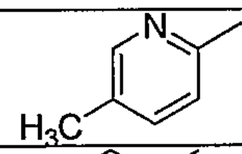
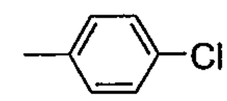
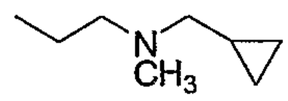
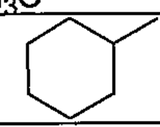
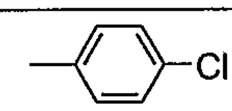
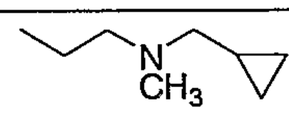
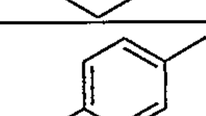
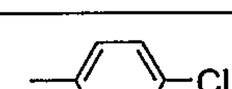
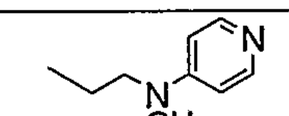
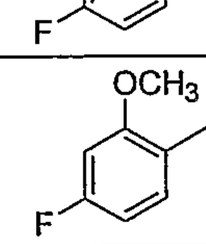
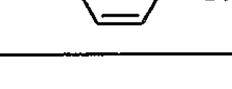
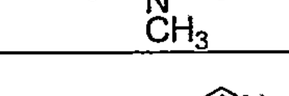
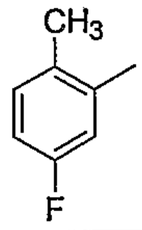
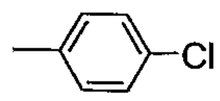
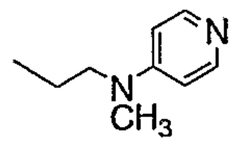
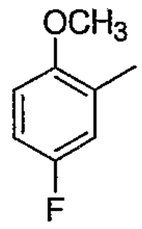
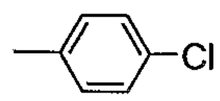
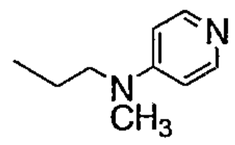
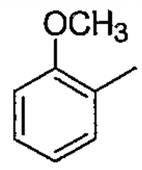
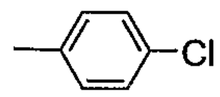
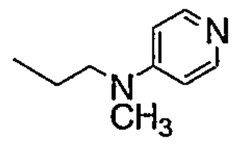
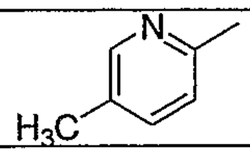
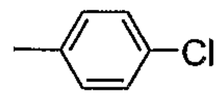
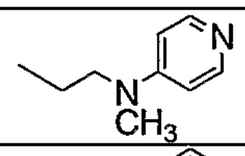
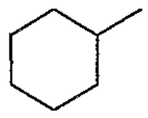
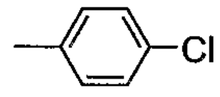
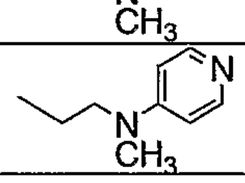
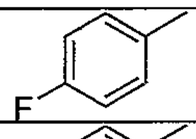
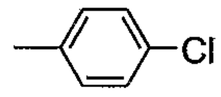
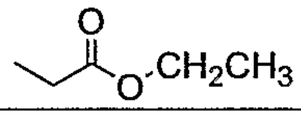
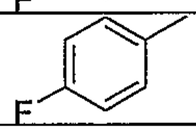
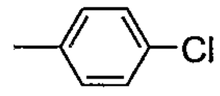
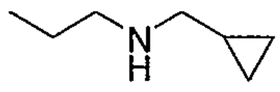
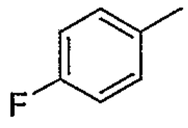
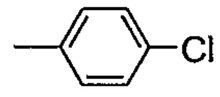
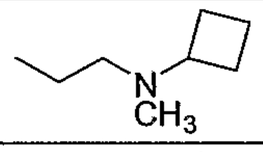
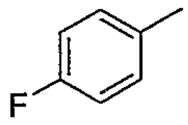
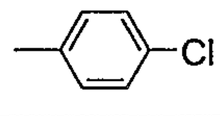
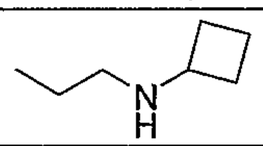
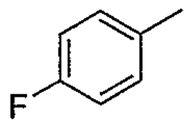
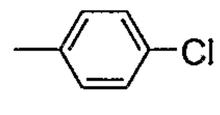
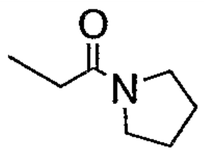
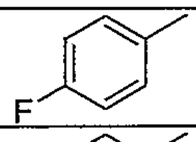
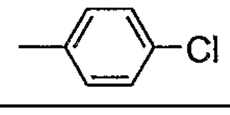
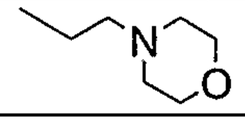
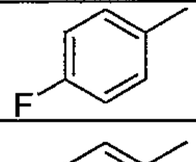
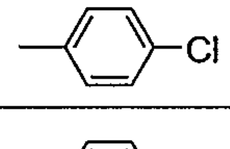
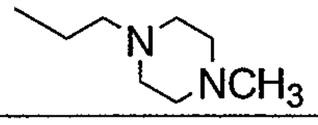
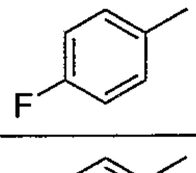
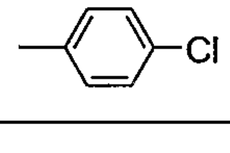
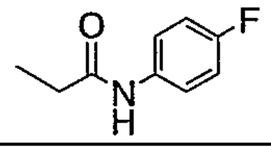
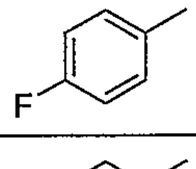
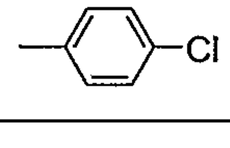
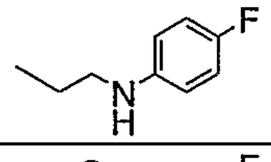
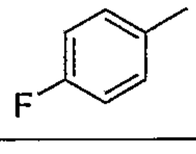
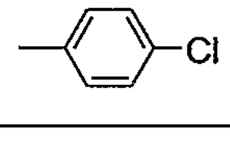
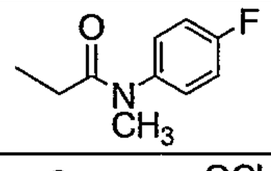
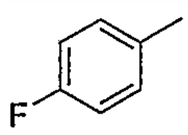
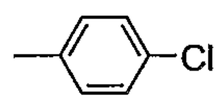
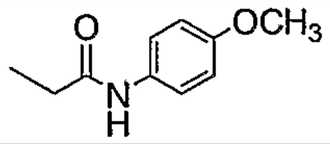
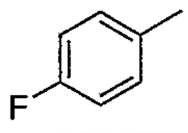
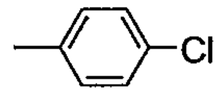
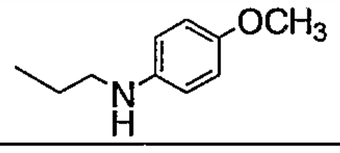
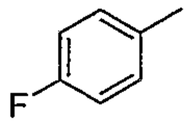
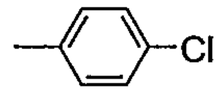
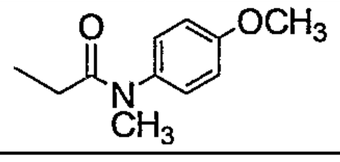
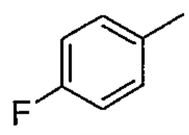
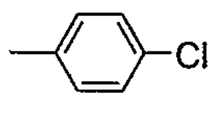
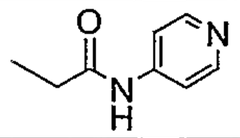
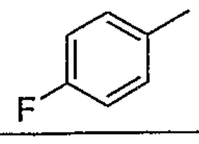
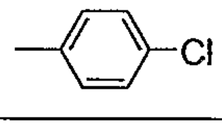
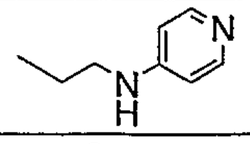
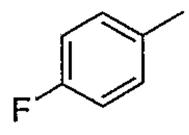
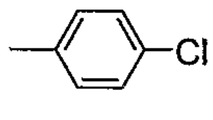
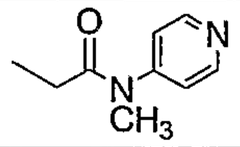
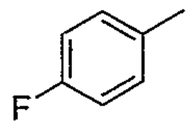
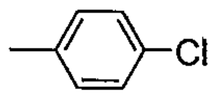
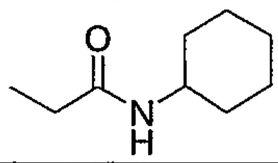
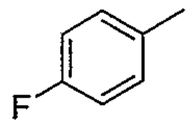
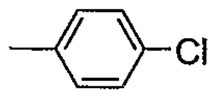
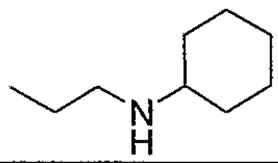
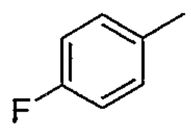
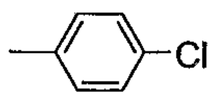
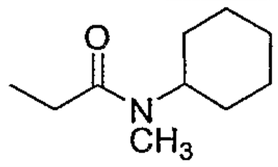
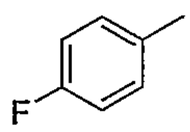
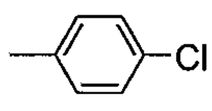
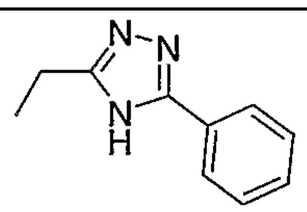
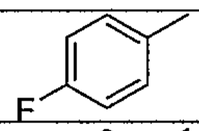
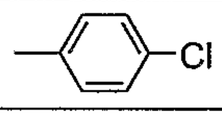
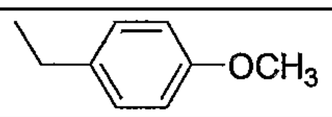
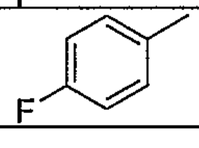
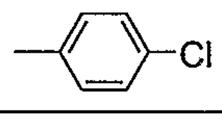
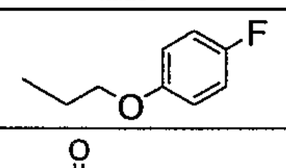
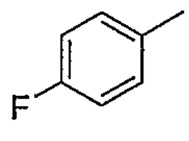
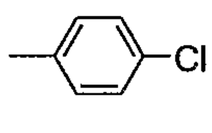
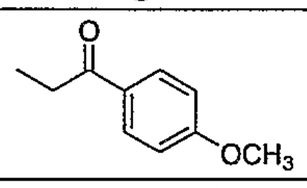
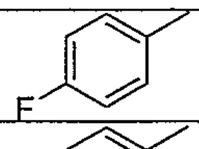
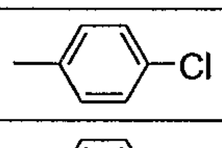
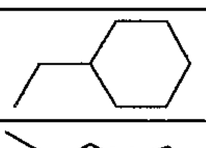
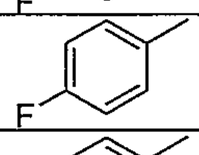
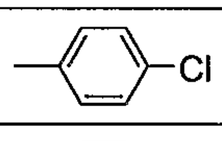
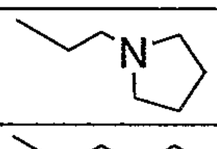
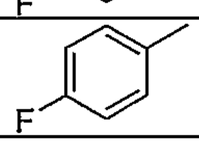
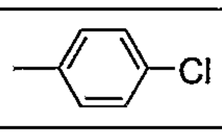
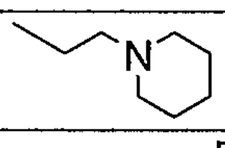
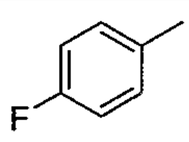
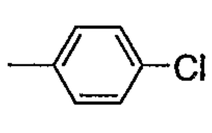
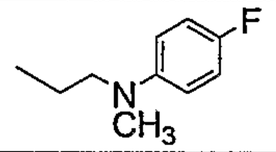
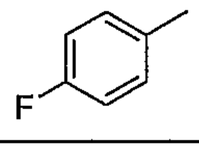
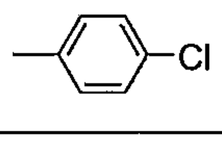
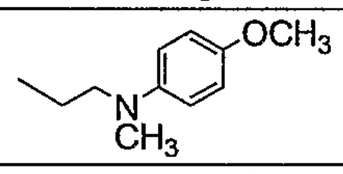
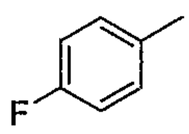
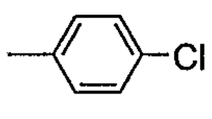
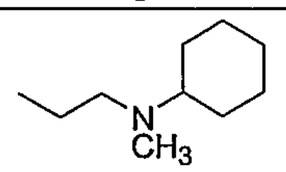
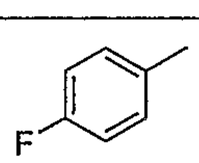
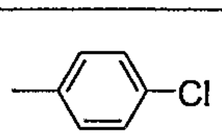
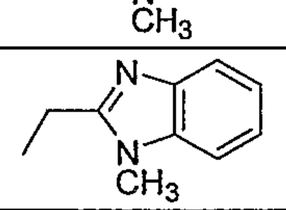
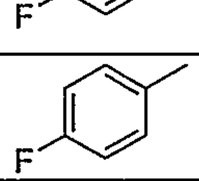
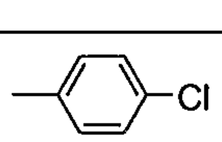
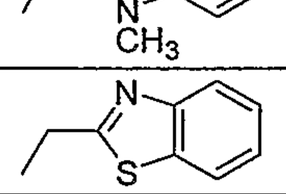
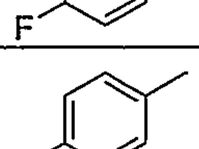
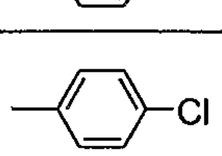
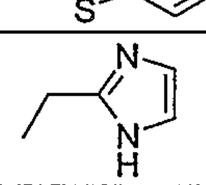
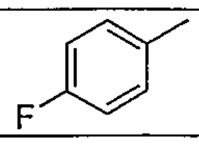
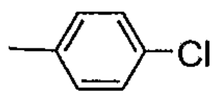
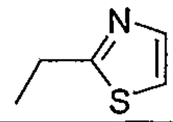
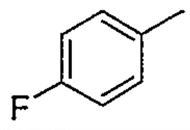
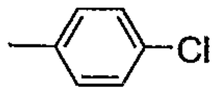
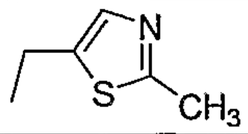
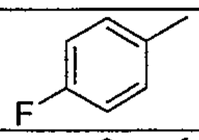
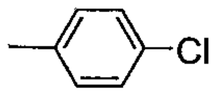
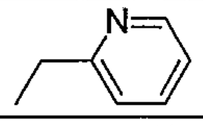
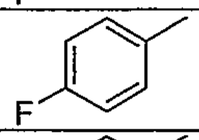
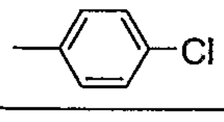
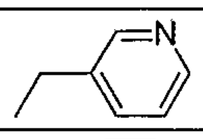
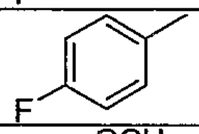
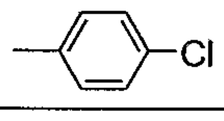
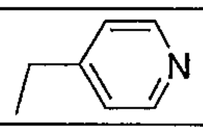
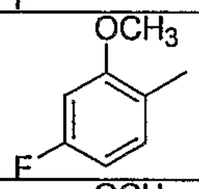
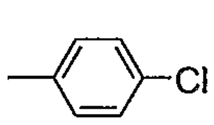
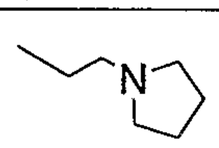
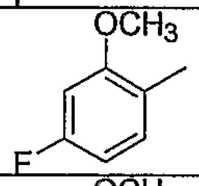
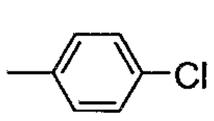
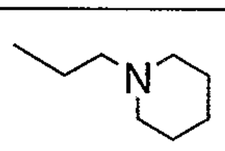
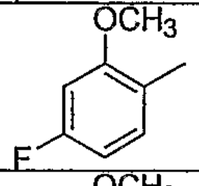
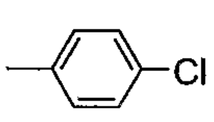
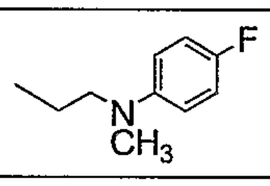
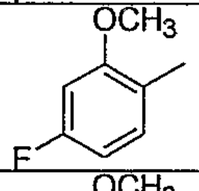
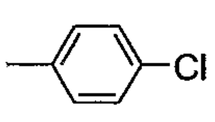
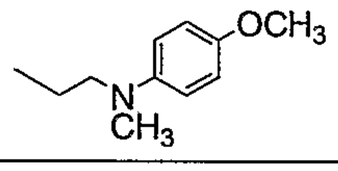
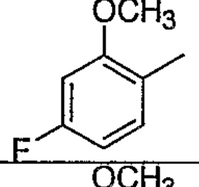
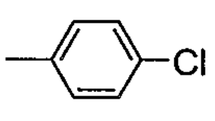
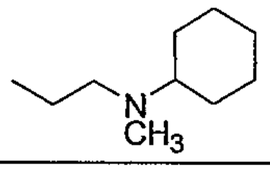
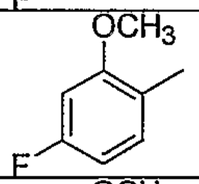
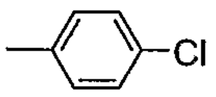
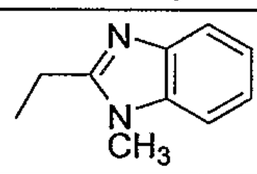
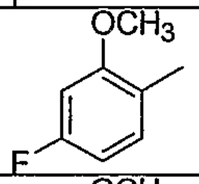
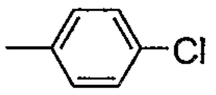
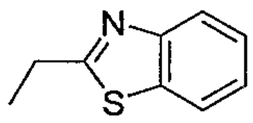
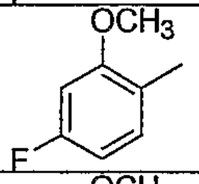
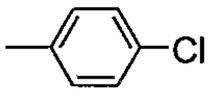
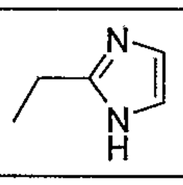
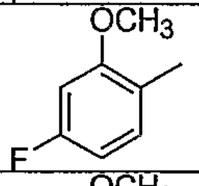
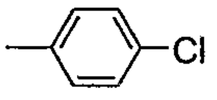
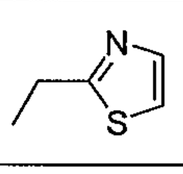
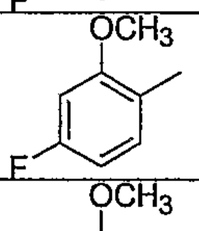
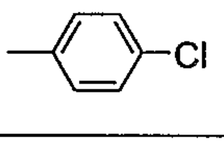
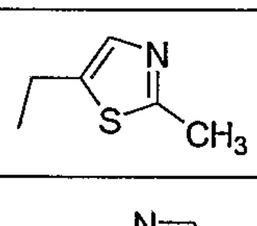
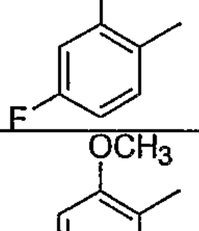
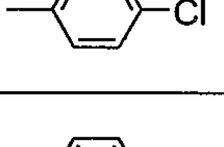
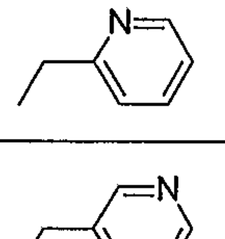
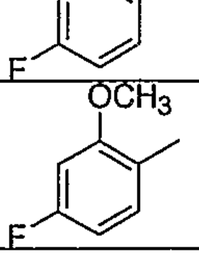
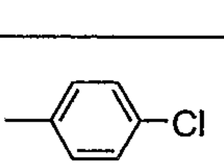
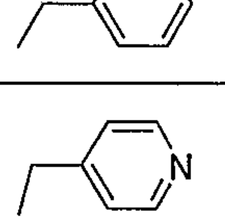
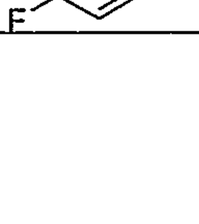


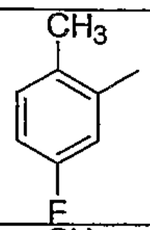
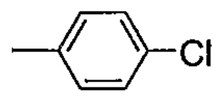
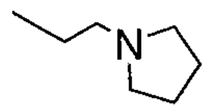
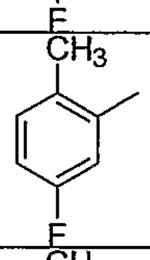
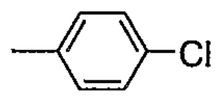
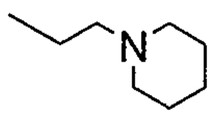
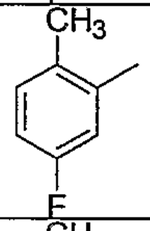
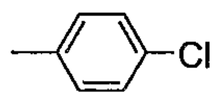
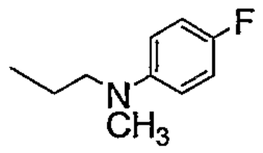
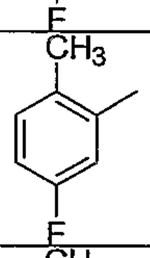
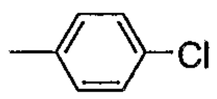
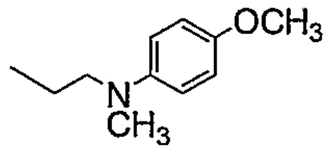
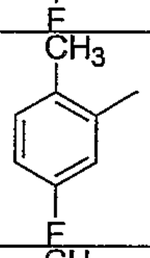
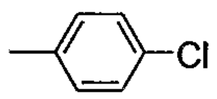
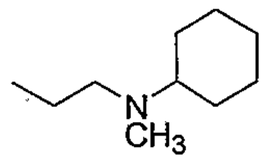
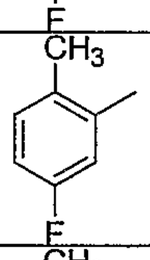
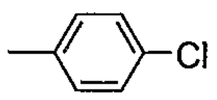
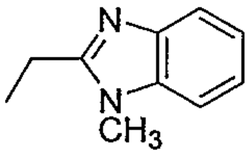
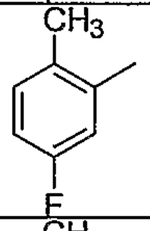
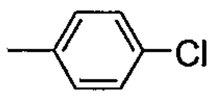
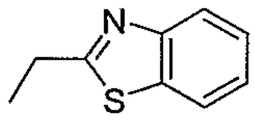
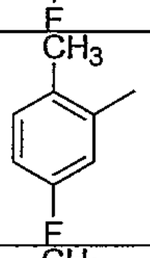
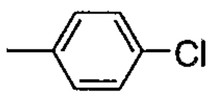
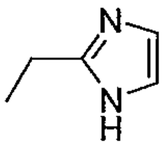
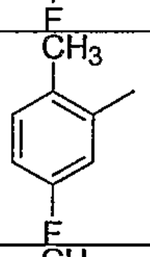
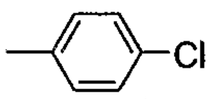
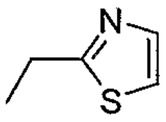
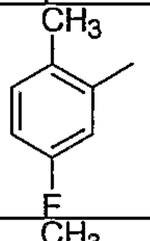
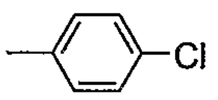
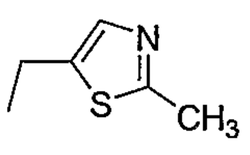
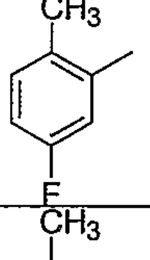
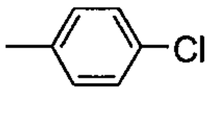
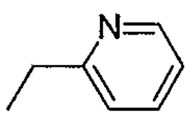
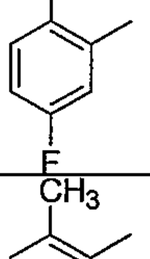
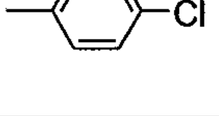
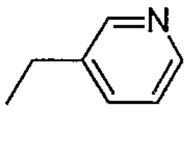
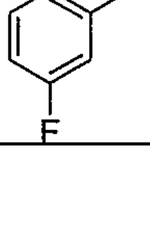
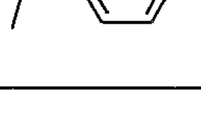
Cpd no.	Ar^1	R^1	R^2

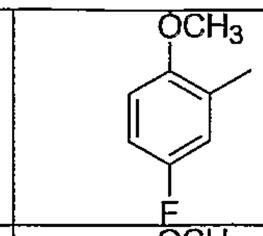
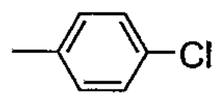
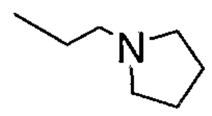
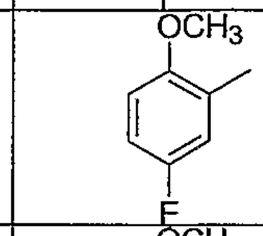
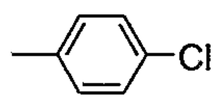
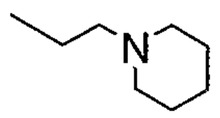
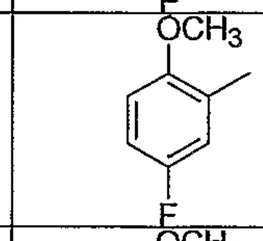
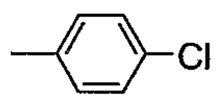
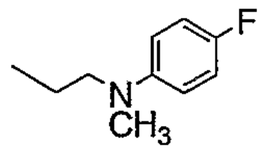
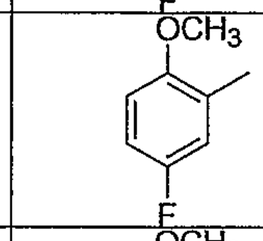
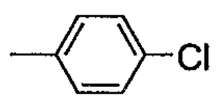
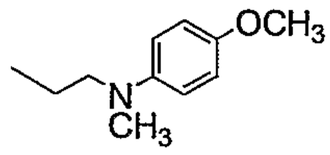
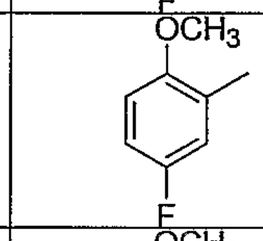
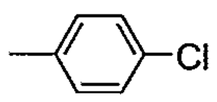
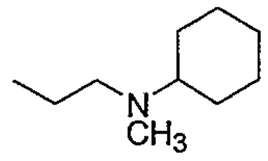
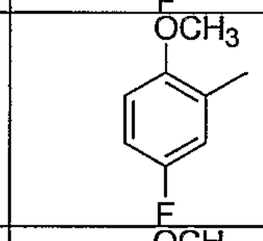
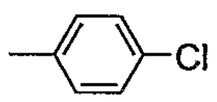
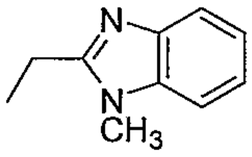
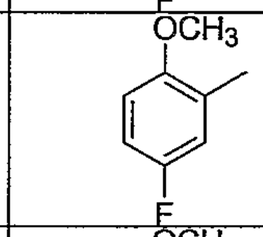
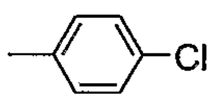
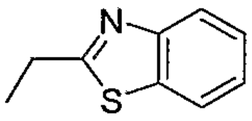
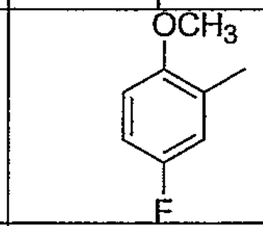
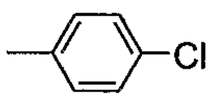
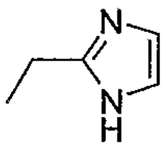
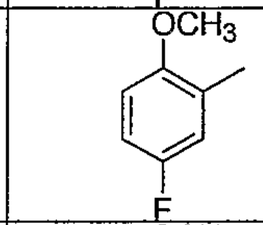
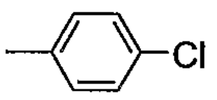
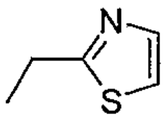
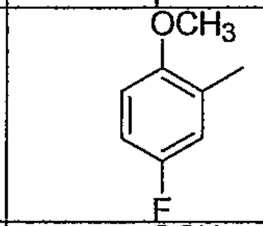
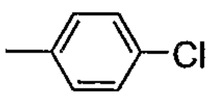
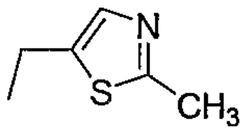
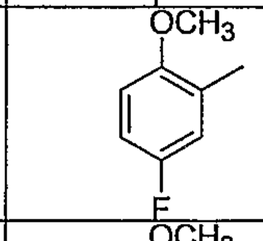
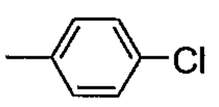
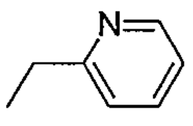
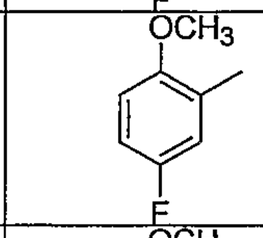
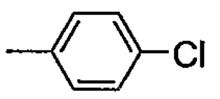
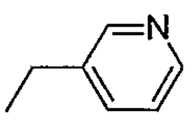
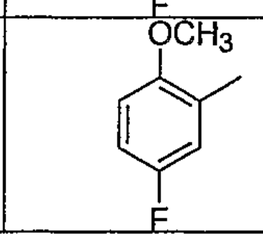
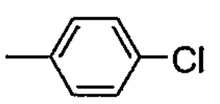
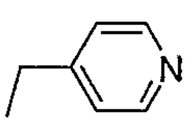
C363			
C364			
C365			
C366			
C367			
C368			
C369			
C370			
C371			
C372			
C373			
C374			
C375			
C376			
C377			
C378			

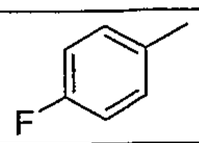
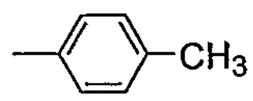
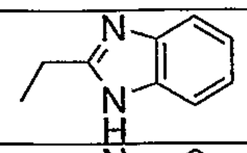
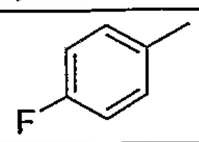
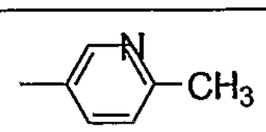
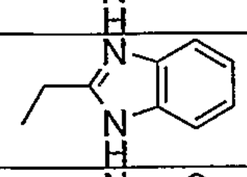
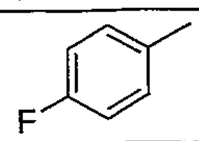
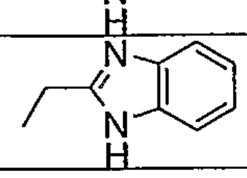
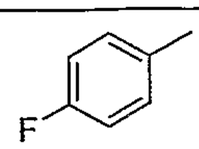
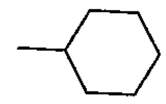
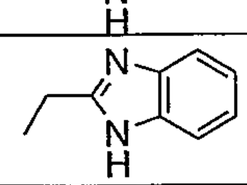
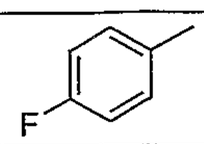
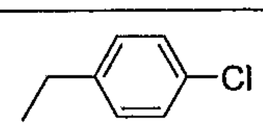
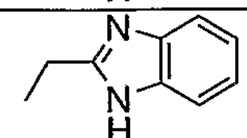
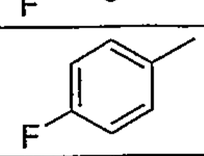
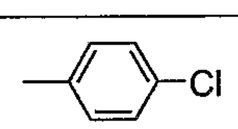
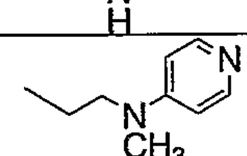
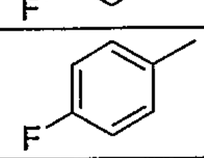
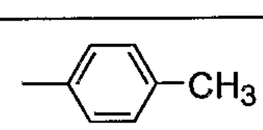
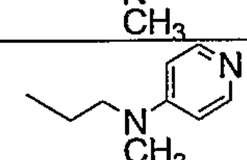
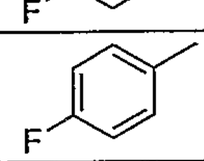
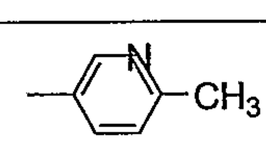
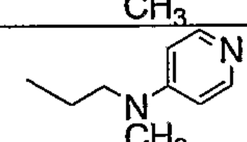
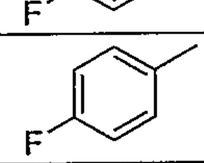
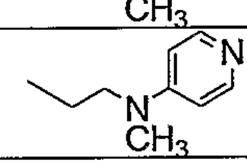
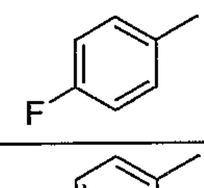
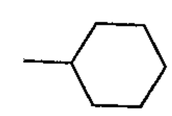
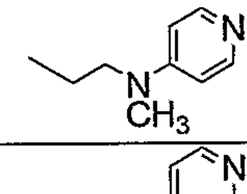
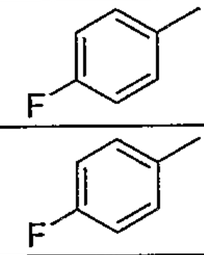
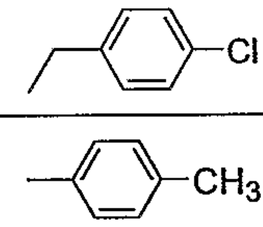
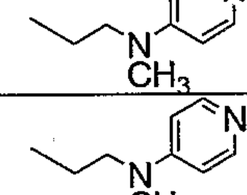
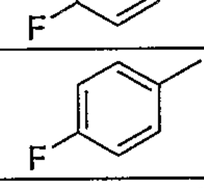
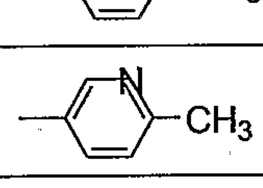
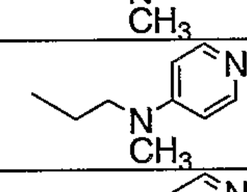
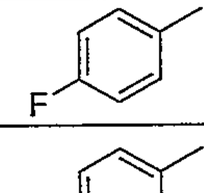
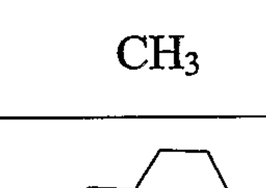
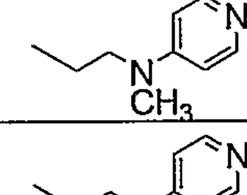
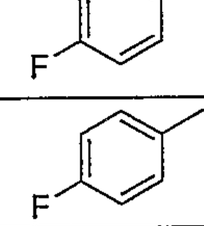
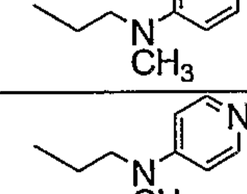
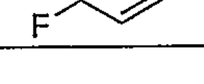
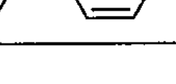
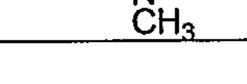
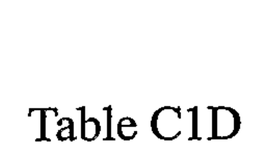
C379			
C380			
C381			
C382			
C383			
C384			
C385			
C386			
C387			
C388			
C389			
C390			
C391			
C392			
C393			
C394			
C395			
C396			

C397			
C398			
C399			
C400			
C401			
C402			
C403			
C404			
C405			
C406			
C407			
C408			
C409			
C410			
C411			
C412			
C413			
C414			
C415			

C416			
C417			
C418			
C419			
C420			
C421			
C422			
C423			
C424			
C425			
C426			
C427			
C428			
C429			
C430			
C431			
C432			
C433			

C434			
C435			
C436			
C437			
C438			
C439			
C440			
C441			
C442			
C443			
C444			
C445			
C446			

C447			
C448			
C449			
C450			
C451			
C452			
C453			
C454			
C455			
C456			
C457			
C458			
C459			

C460			
C461			
C462		CH_3	
C463			
C464			
C465			
C466			
C467			
C468		CH_3	
C469			
C470			
C471			
C472			
C473		CH_3	
C474			
C475			

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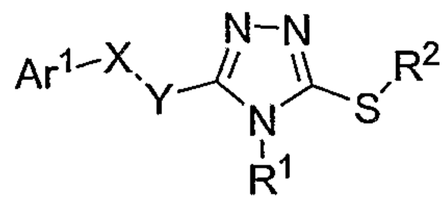
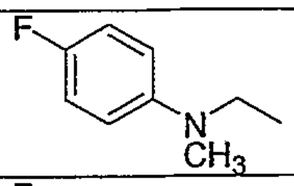
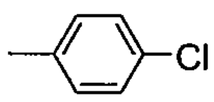
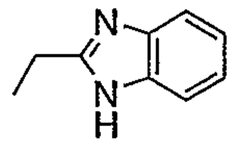
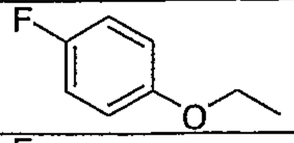
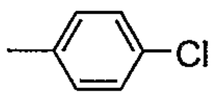
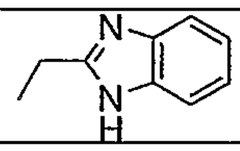
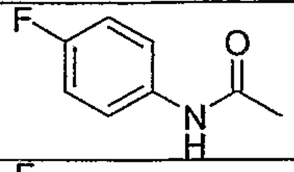
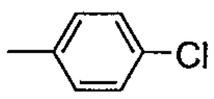
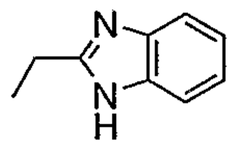
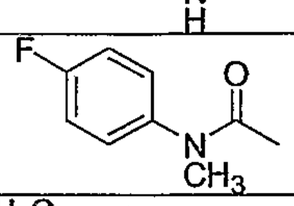
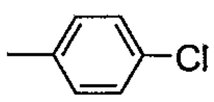
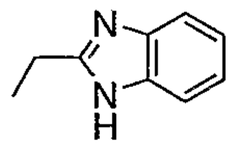
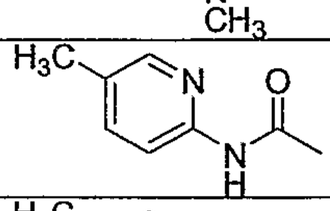
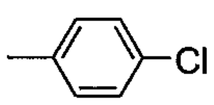
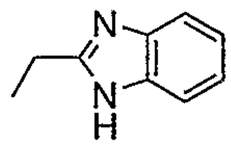
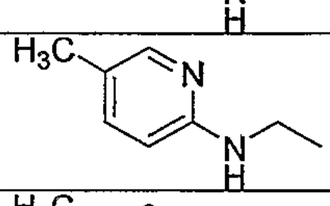
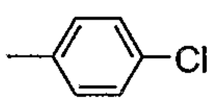
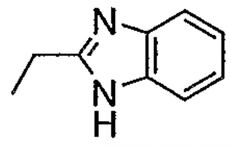
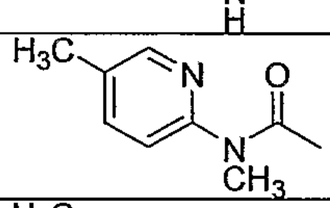
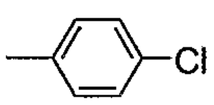
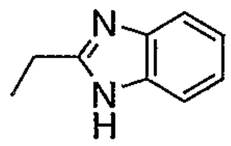
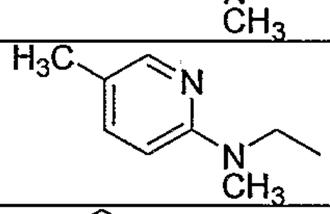
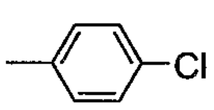
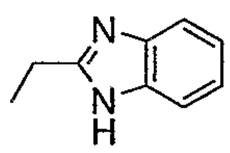
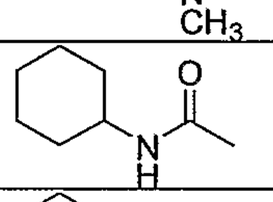
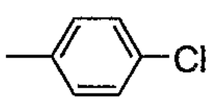
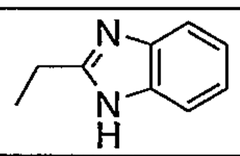
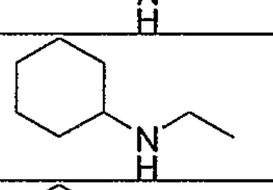
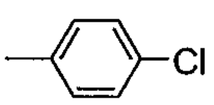
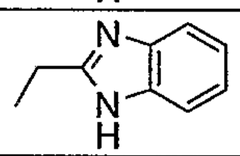
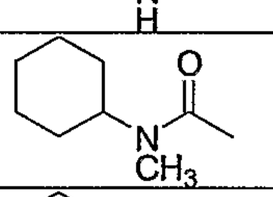
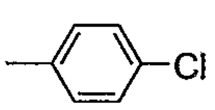
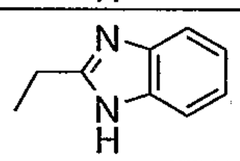
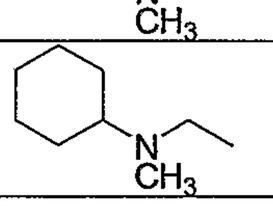
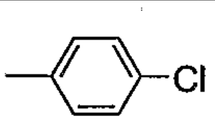
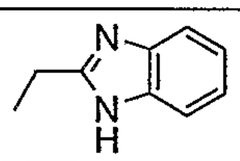
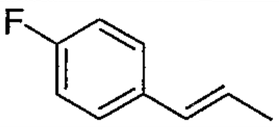
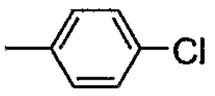
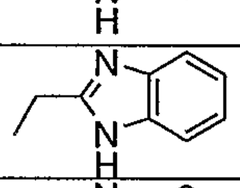
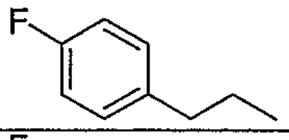
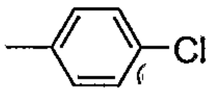
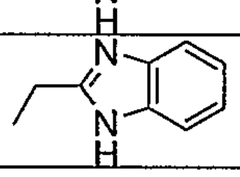
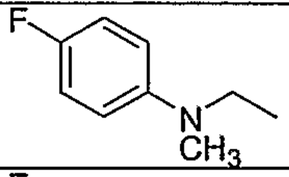
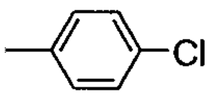
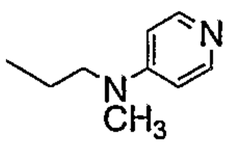
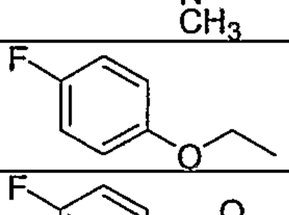
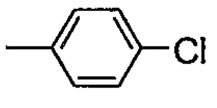
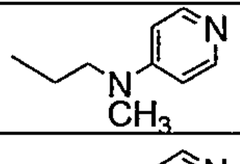
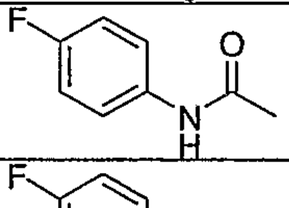
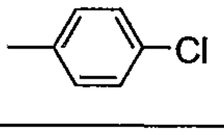
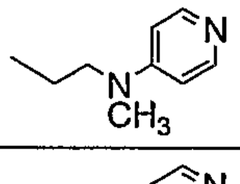
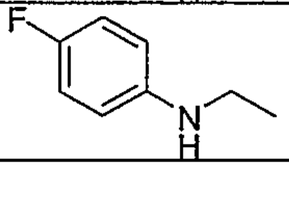
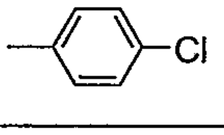
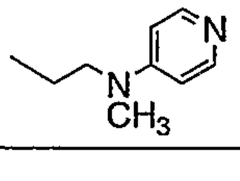
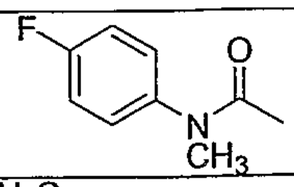
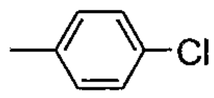
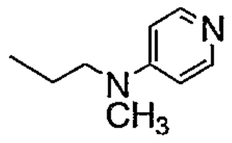
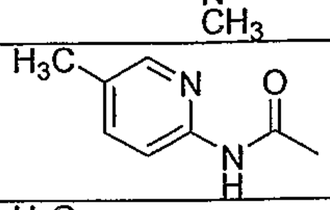
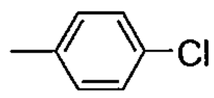
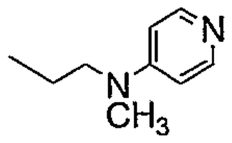
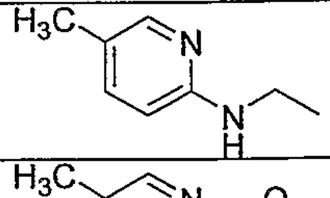
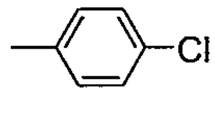
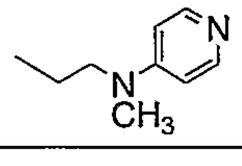
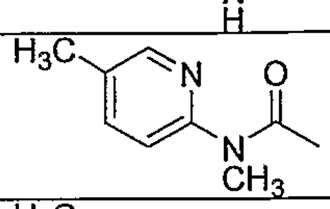
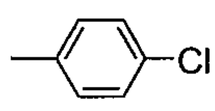
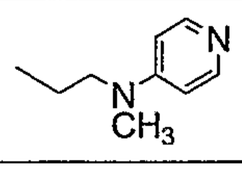
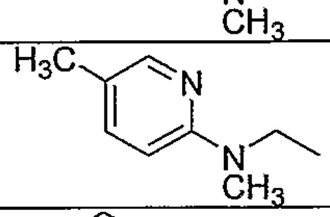
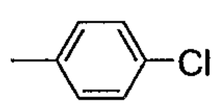
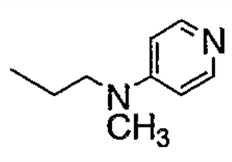
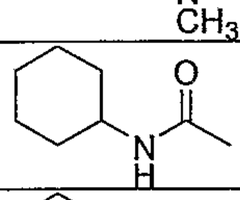
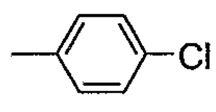
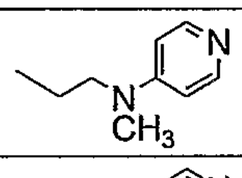
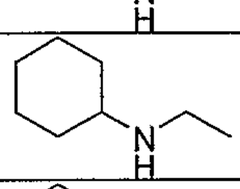
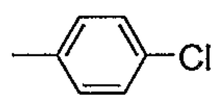
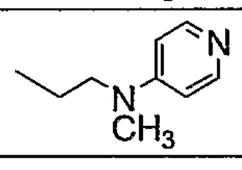
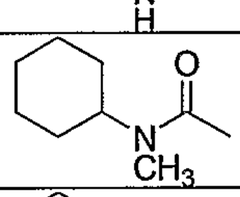
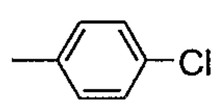
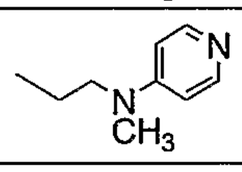
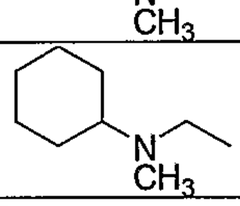
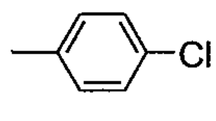
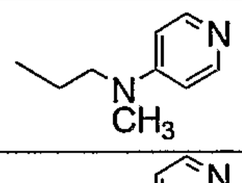
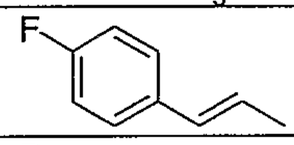
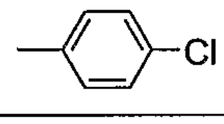
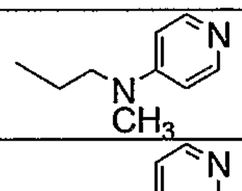
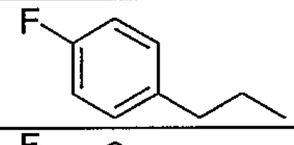
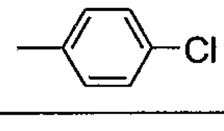
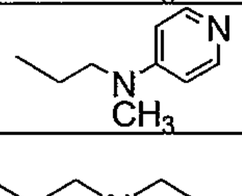
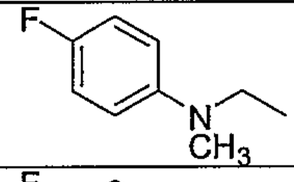
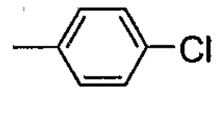
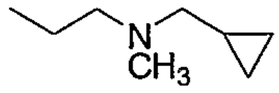
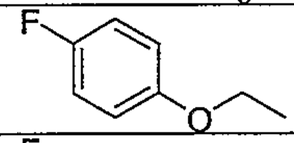
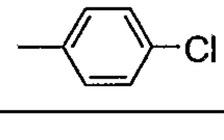
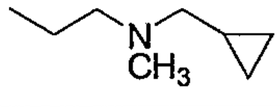
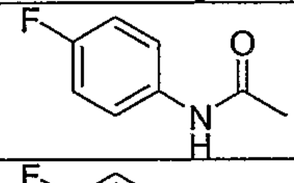
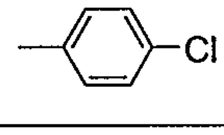
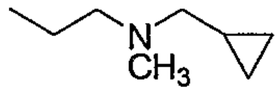
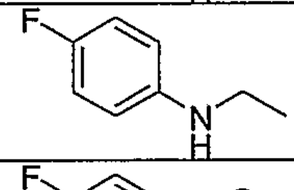
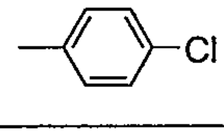
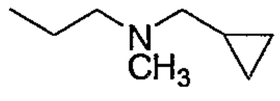
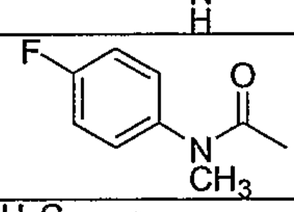
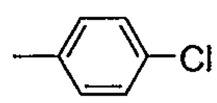
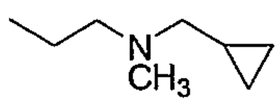
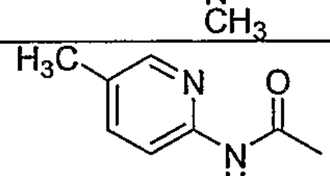
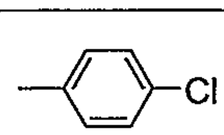
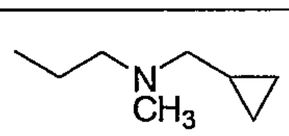
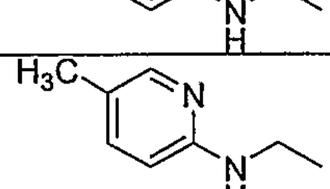
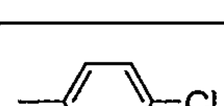
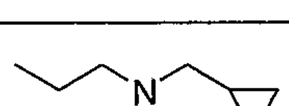
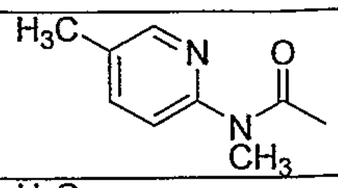
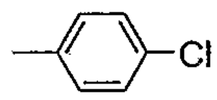
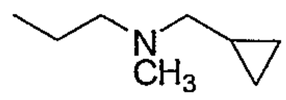
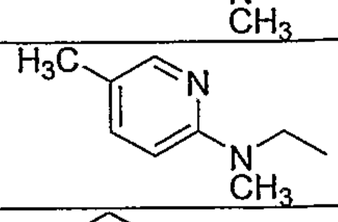
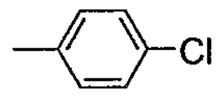
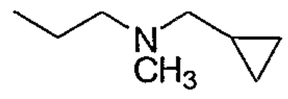
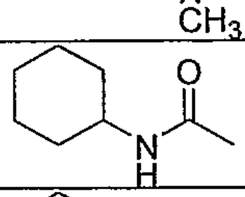
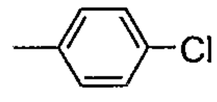
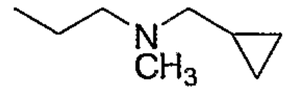
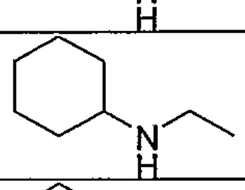
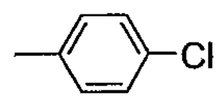
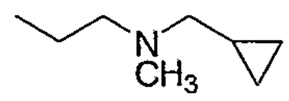
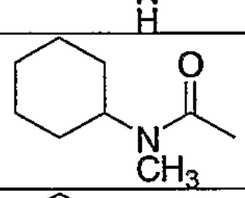
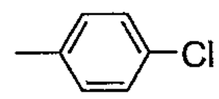
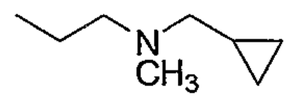
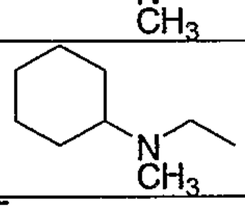
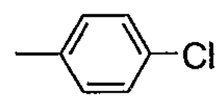
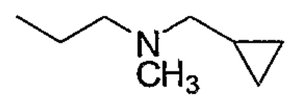
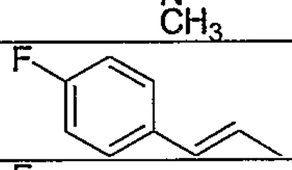
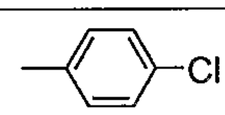
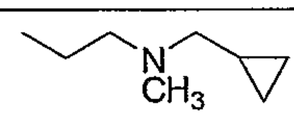
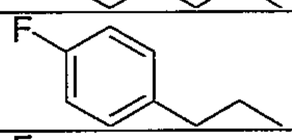
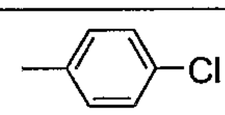
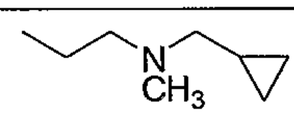
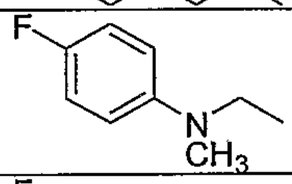
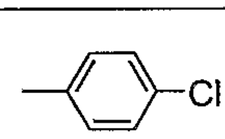
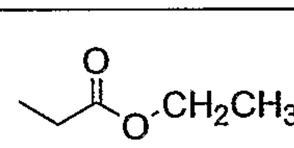
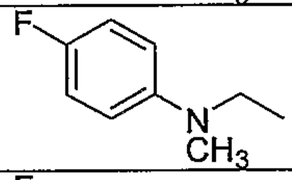
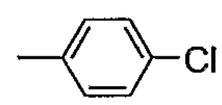
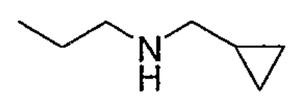
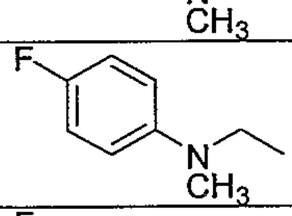
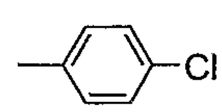
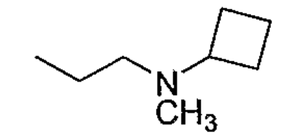
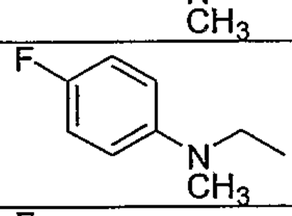
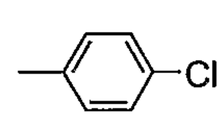
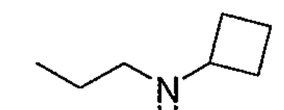
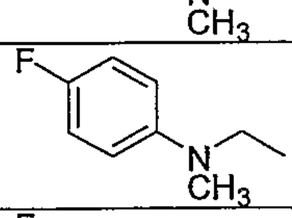
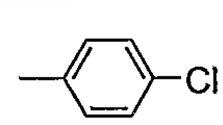
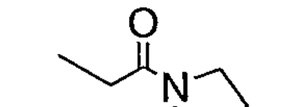
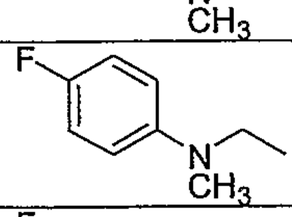
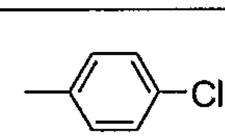
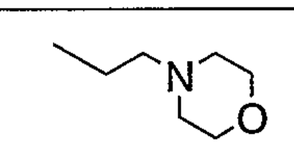
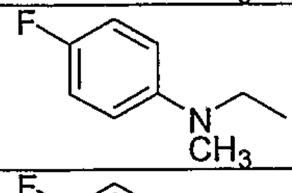
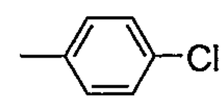
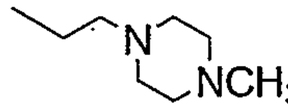
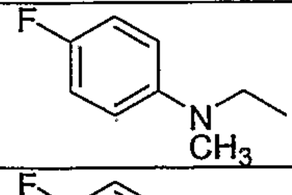
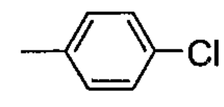
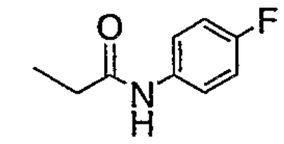
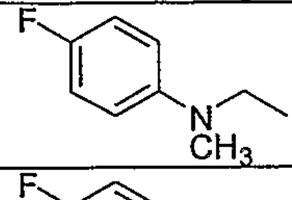
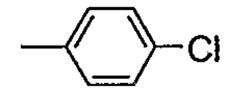
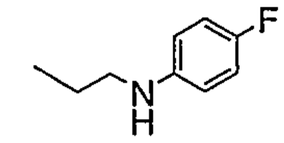
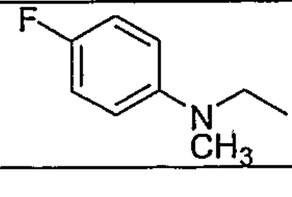
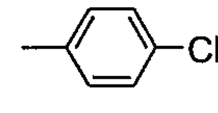
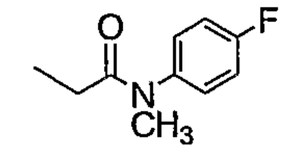
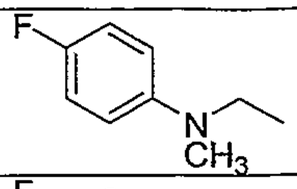
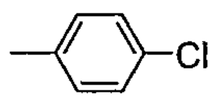
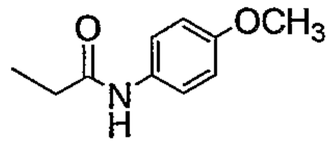
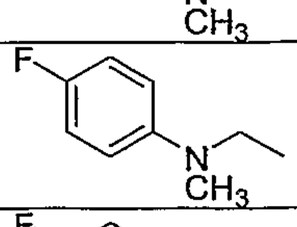
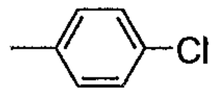
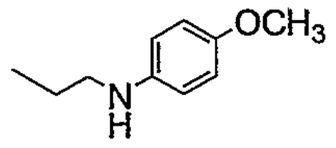
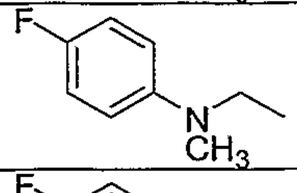
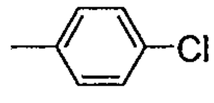
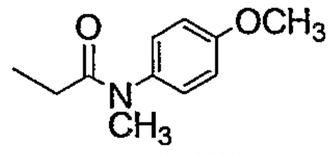
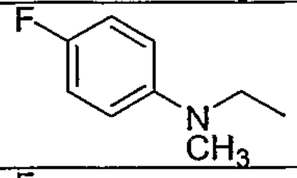
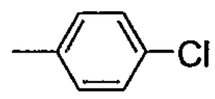
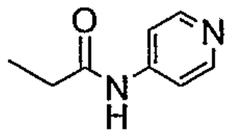
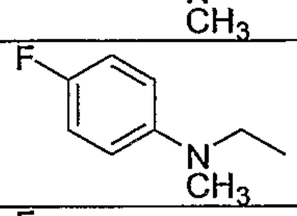
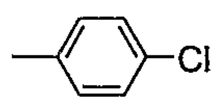
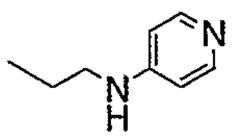
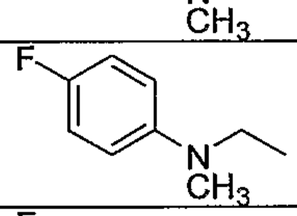
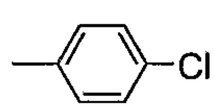
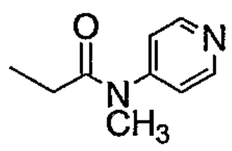
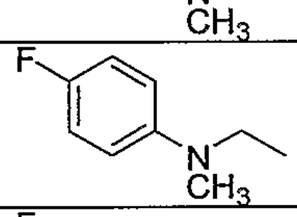
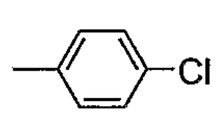
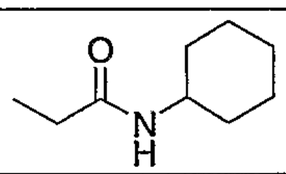
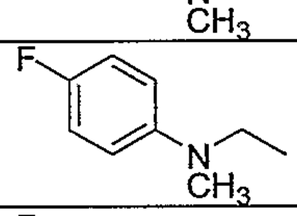
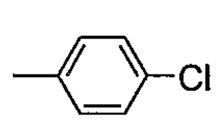
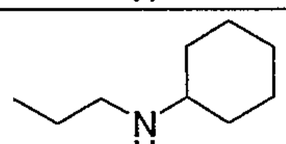
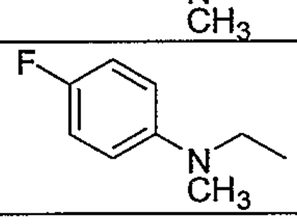
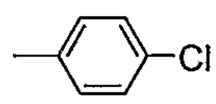
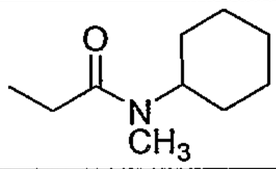
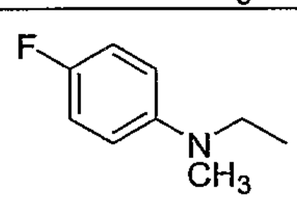
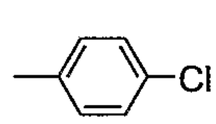
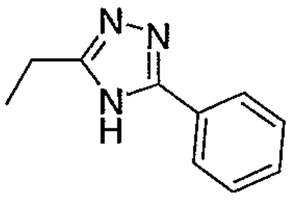
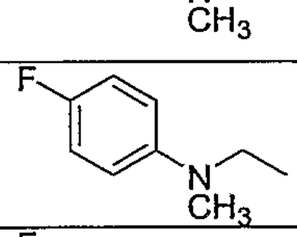
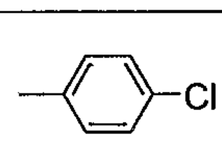
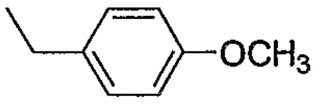
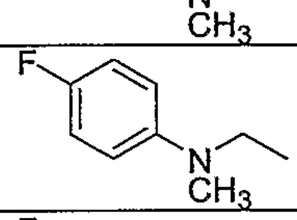
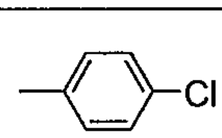
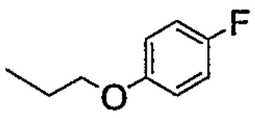
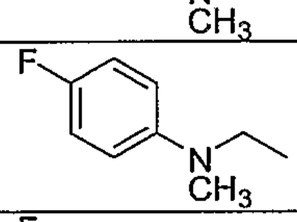
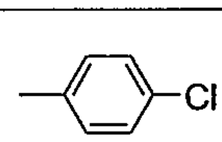
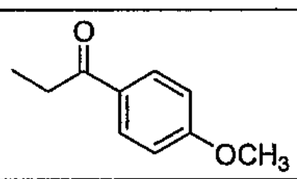
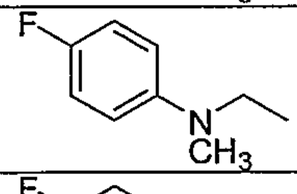
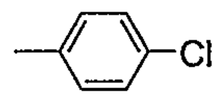
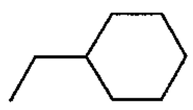
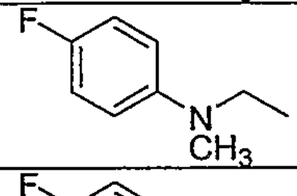
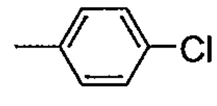
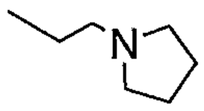
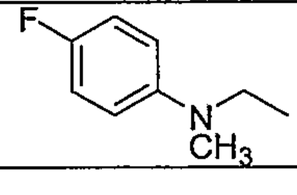
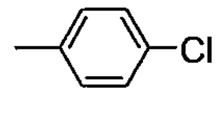
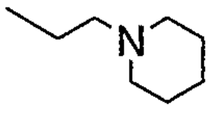


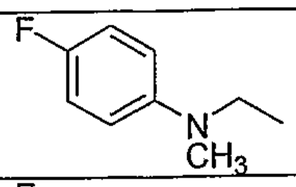
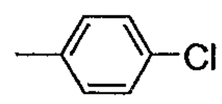
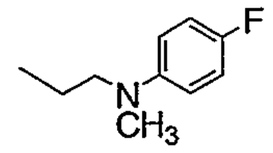
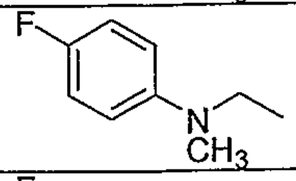
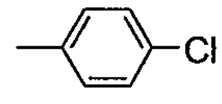
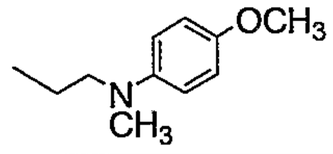
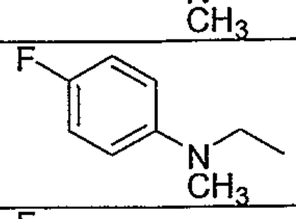
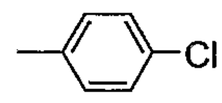
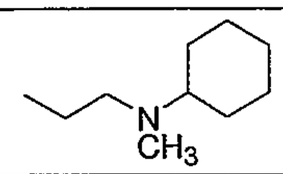
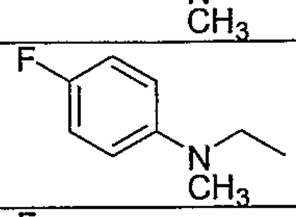
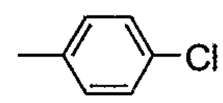
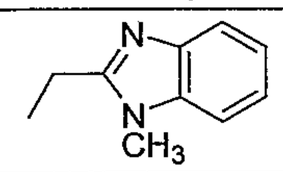
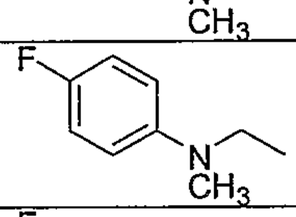
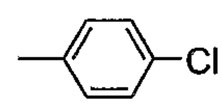
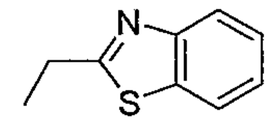
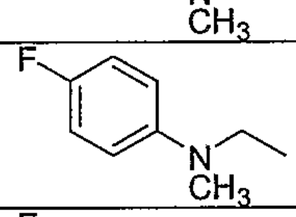
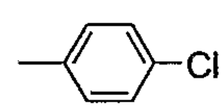
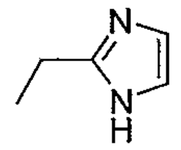
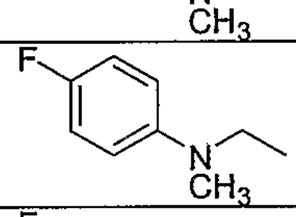
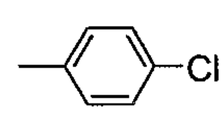
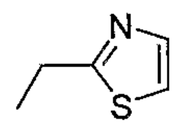
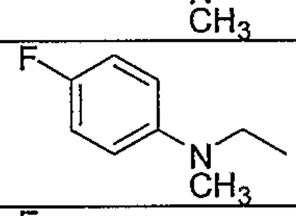
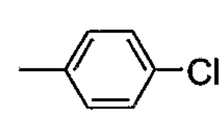
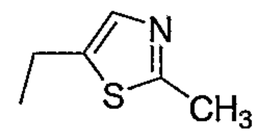
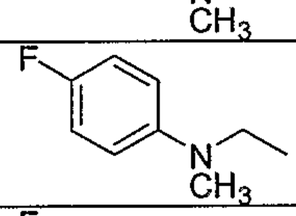
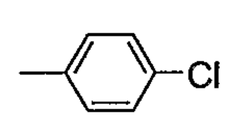
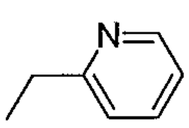
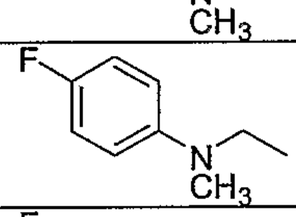
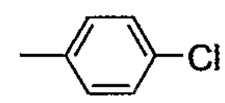
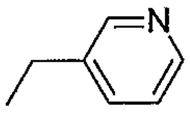
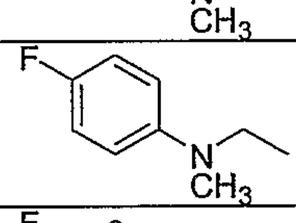
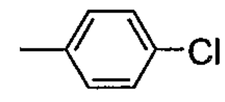
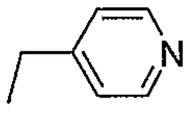
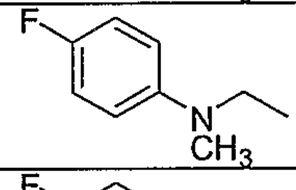
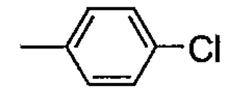
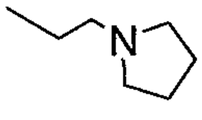
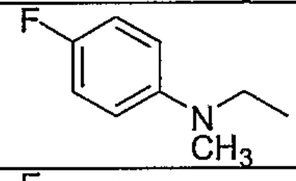
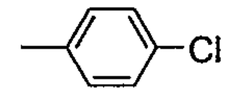
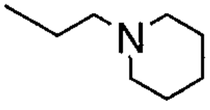
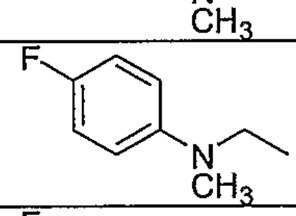
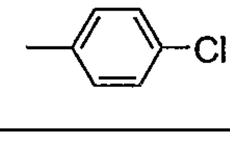
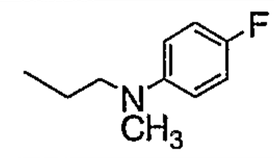
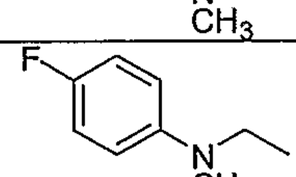
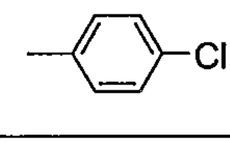
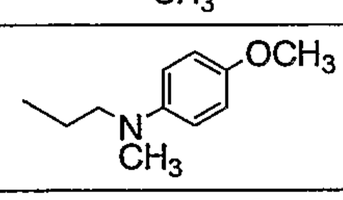
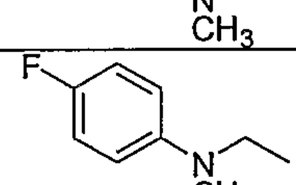
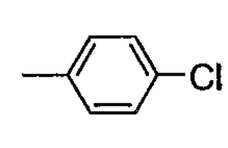
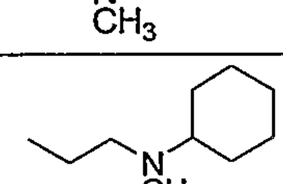
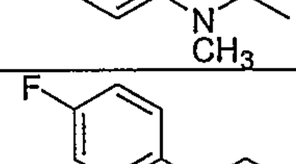
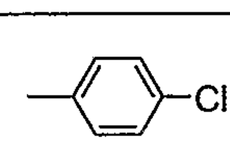
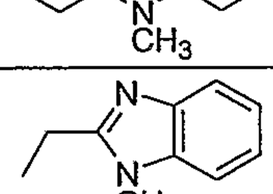
Cpd no.	Ar^1-X-Y	R^1	R^2

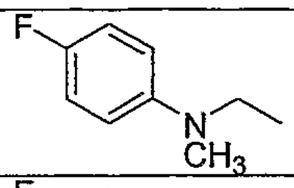
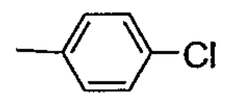
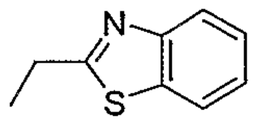
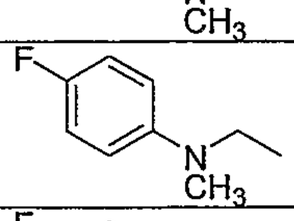
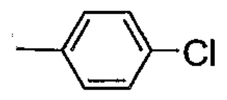
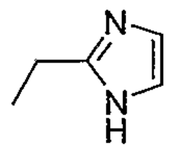
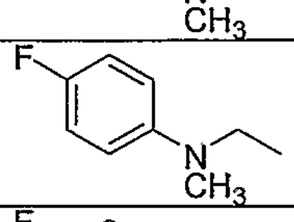
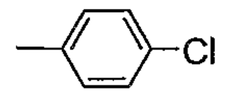
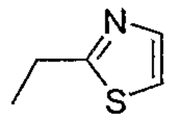
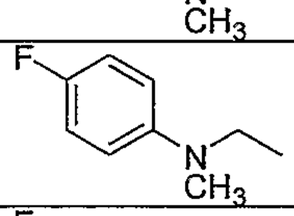
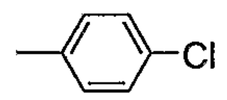
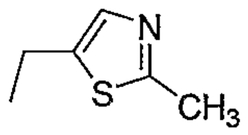
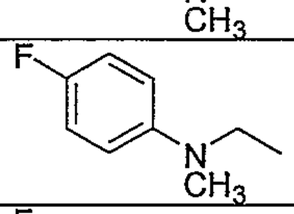
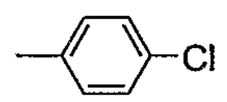
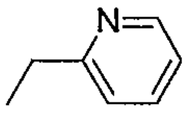
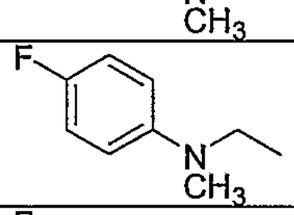
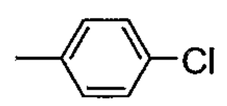
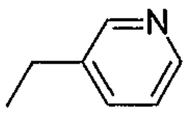
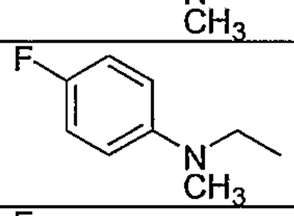
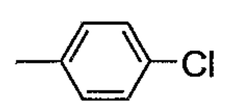
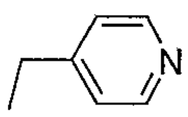
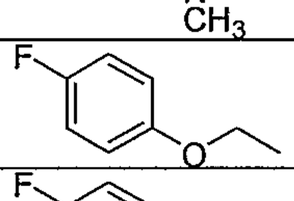
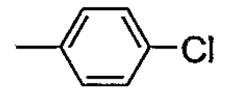
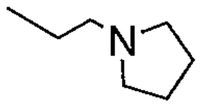
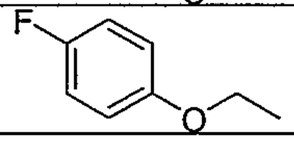
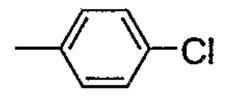
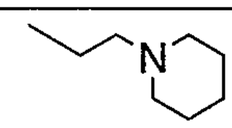
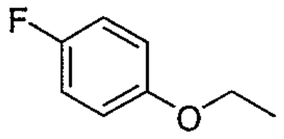
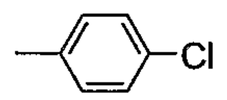
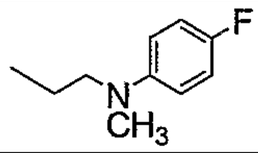
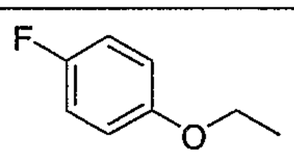
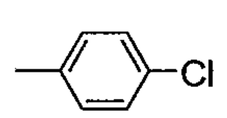
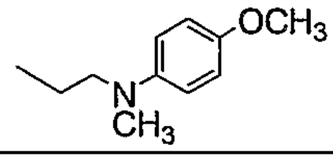
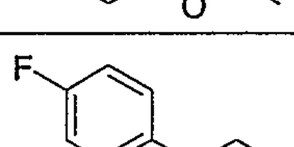
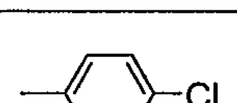
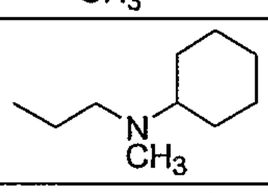
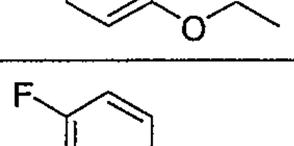
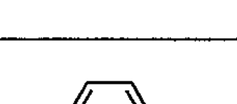
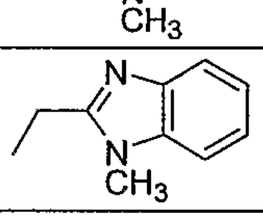
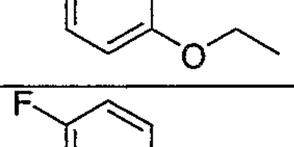
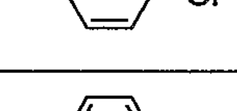
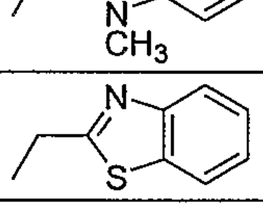
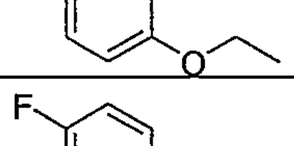
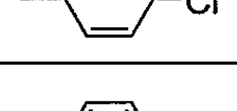
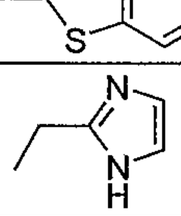
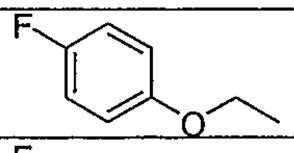
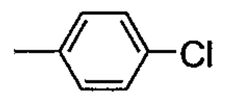
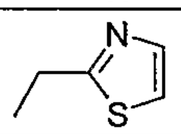
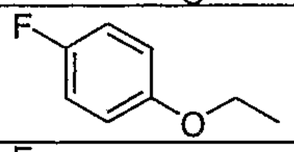
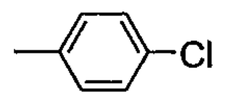
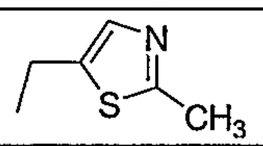
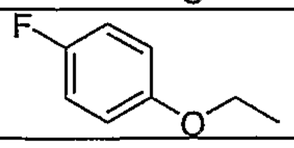
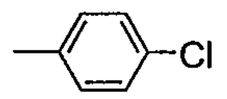
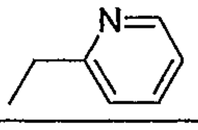
C476			
C477			
C478			
C479			
C480			
C481			
C482			
C483			
C484			
C485			
C486			
C487			
C488			
C489			
C490			
C491			
C492			
C493			

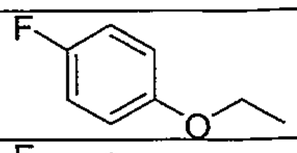
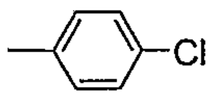
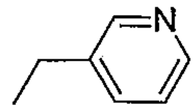
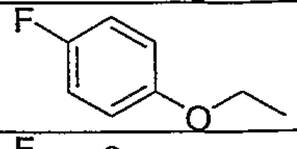
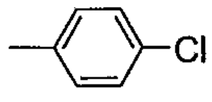
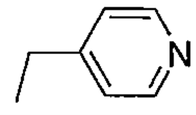
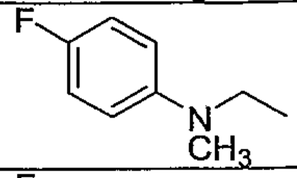
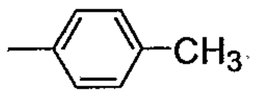
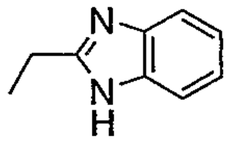
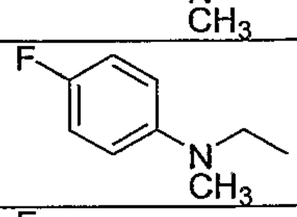
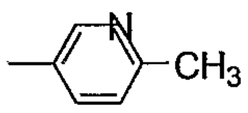
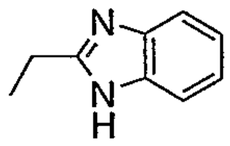
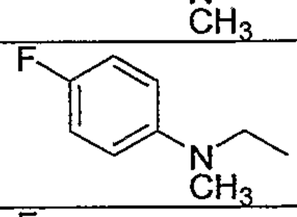
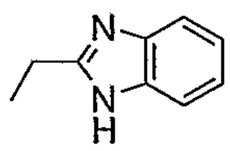
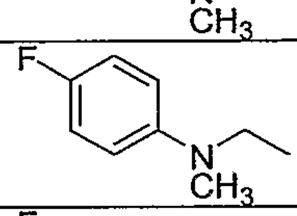
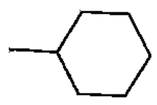
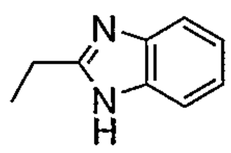
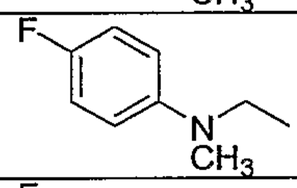
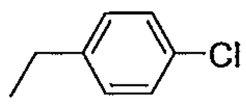
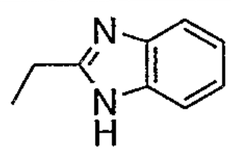
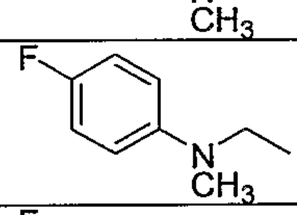
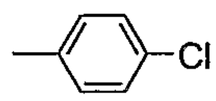
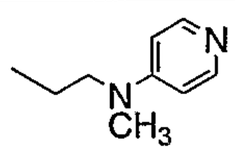
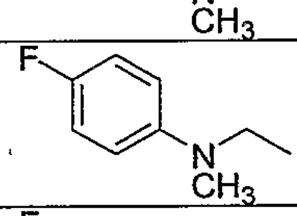
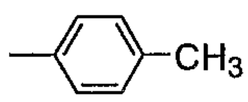
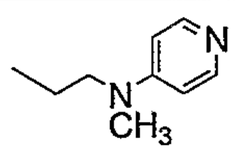
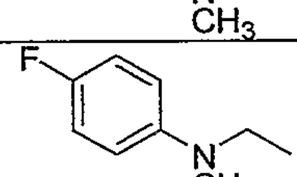
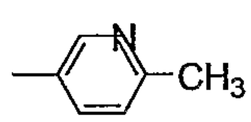
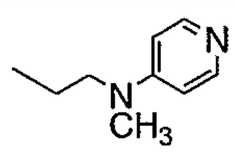
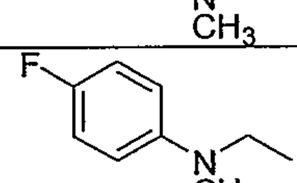
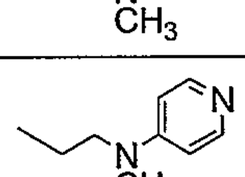
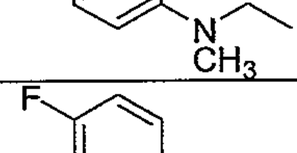
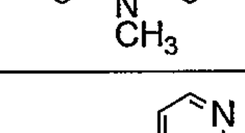
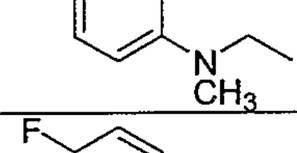
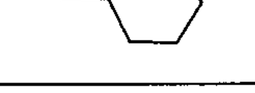
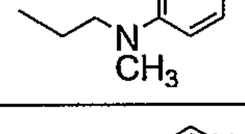
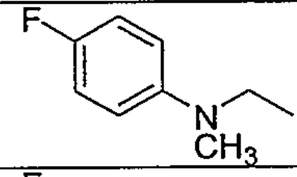
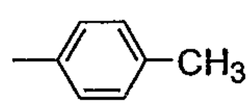
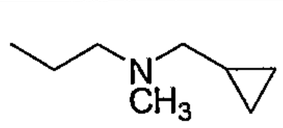
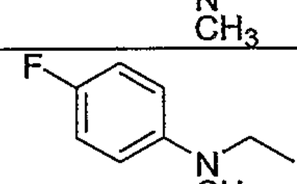
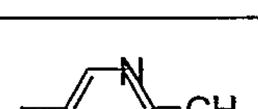
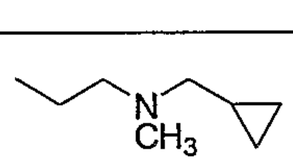
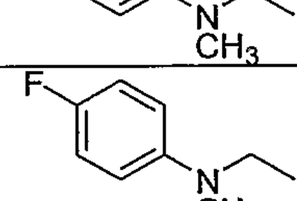
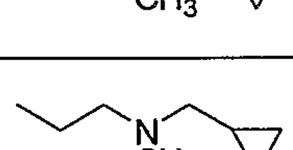
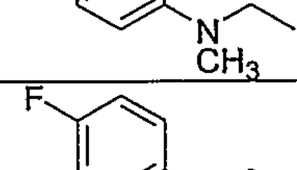
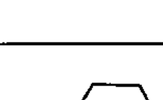
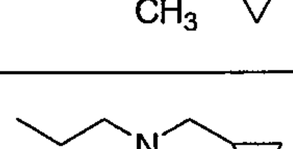
C494			
C495			
C496			
C497			
C498			
C499			
C500			
C501			
C502			
C503			
C504			
C505			
C506			
C507			
C508			
C509			
C510			
C511			

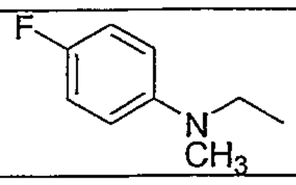
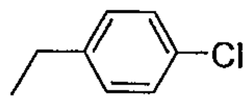
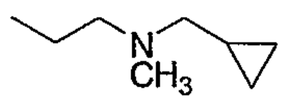
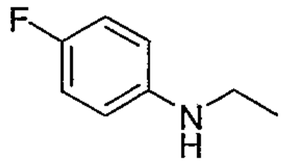
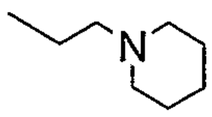
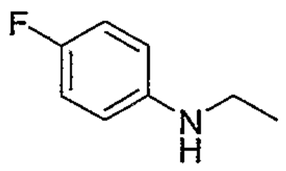
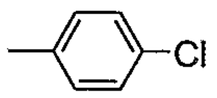
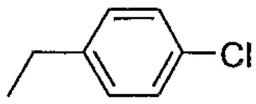
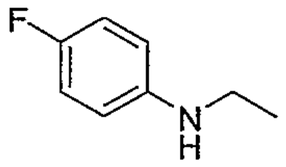
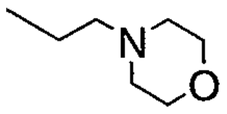
C512			
C513			
C514			
C515			
C516			
C517			
C518			
C519			
C520			
C521			
C522			
C523			
C524			
C525			
C526			
C527			
C528			
C529			

C530			
C531			
C532			
C533			
C534			
C535			
C536			
C537			
C538			
C539			
C540			
C541			
C542			
C543			
C544			
C545			

C546			
C547			
C548			
C549			
C550			
C551			
C552			
C553			
C554			
C555			
C556			
C557			
C558			
C559			
C560			
C561			
C562			

C563			
C564			
C565			
C566			
C567			
C568			
C569			
C570			
C571			
C572			
C573			
C574			
C575			
C576			
C577			
C578			
C579			
C580			

C581			
C582			
C583			
C584			
C585		CH_3	
C586			
C587			
C588			
C589			
C590			
C591		CH_3	
C592			
C593			
C594			
C595			
C596		CH_3	
C597			

C598			
C599		CH_3	
C600			
C601		CH_3	

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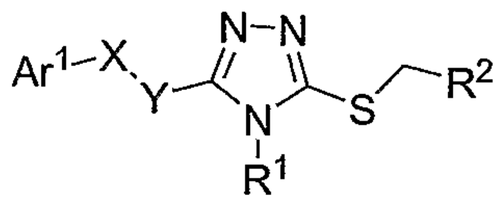

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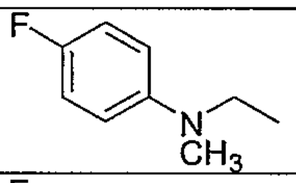
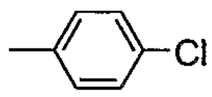
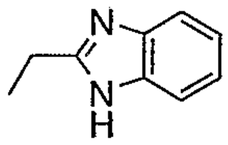
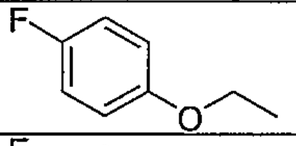
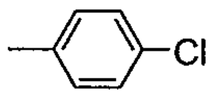
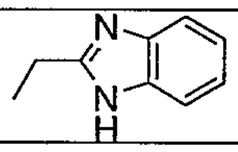
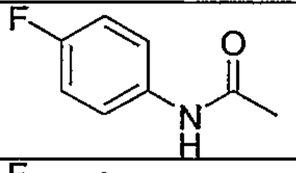
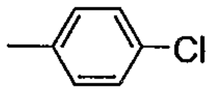
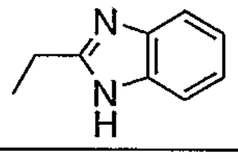
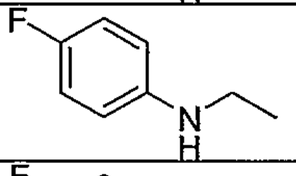
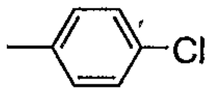
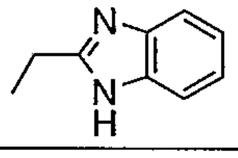
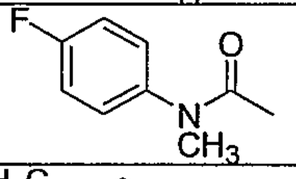
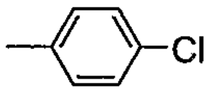
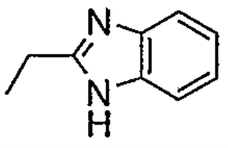
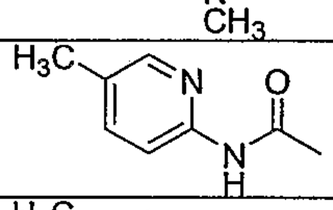
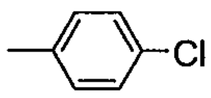
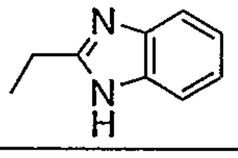
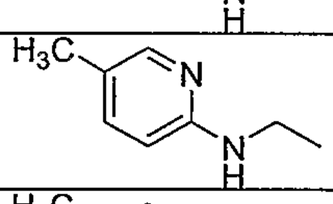
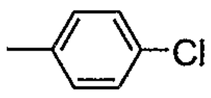
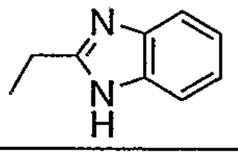
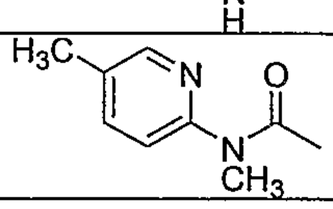
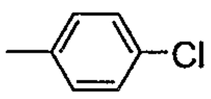
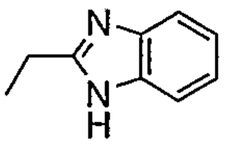
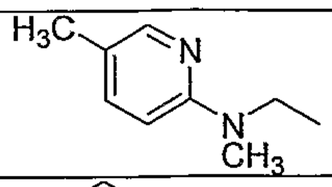
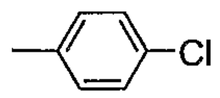
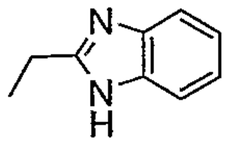
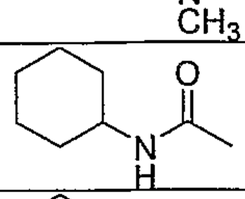
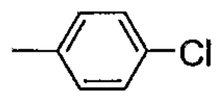
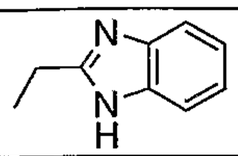
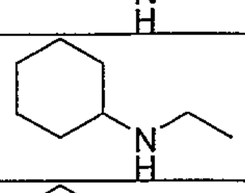
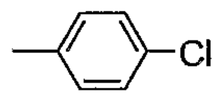
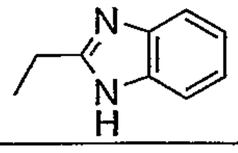
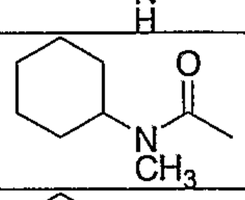
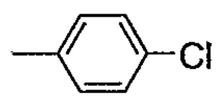
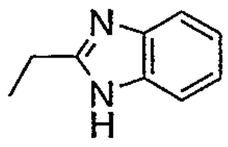
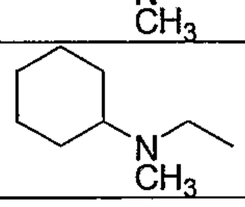
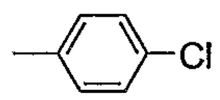
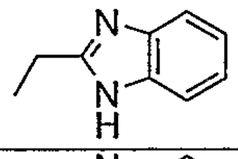
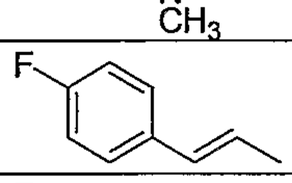
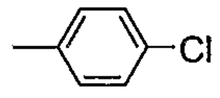
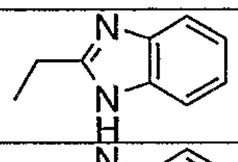
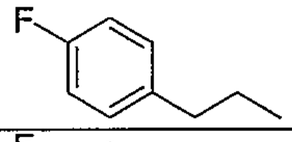
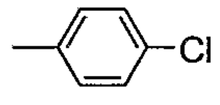
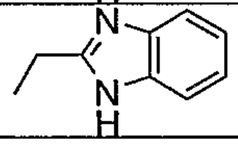
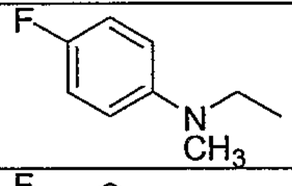
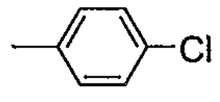
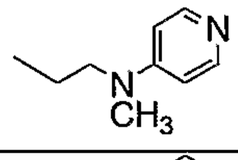
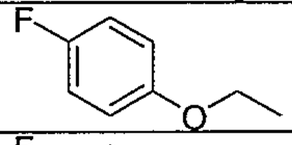
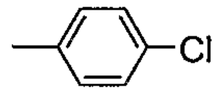
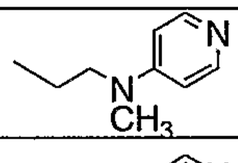
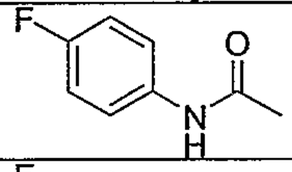
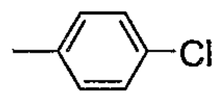
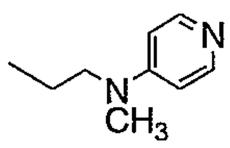
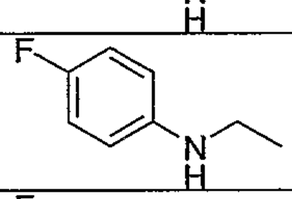
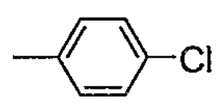
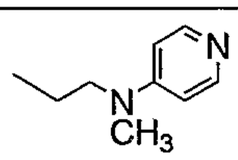
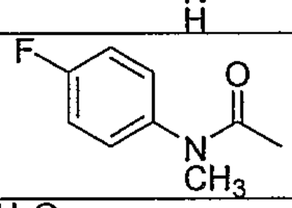
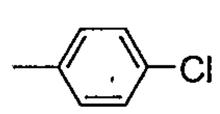
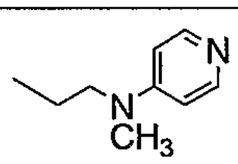
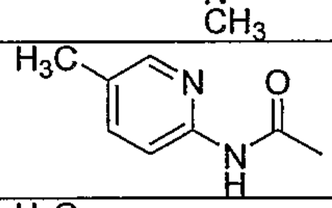
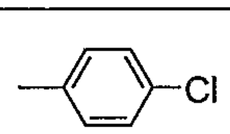
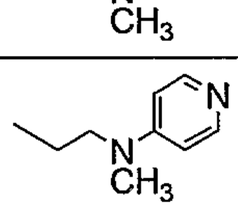
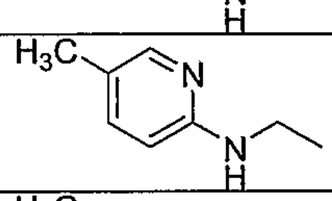
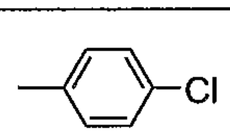
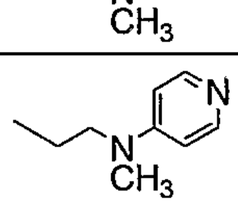
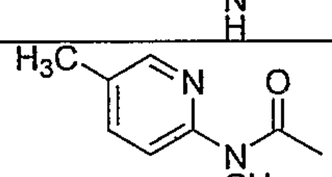
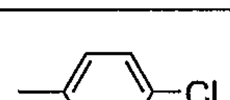
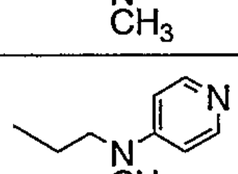
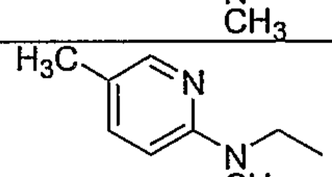
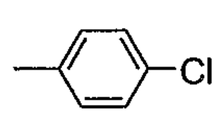
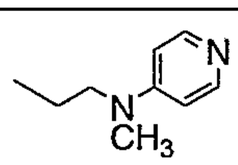
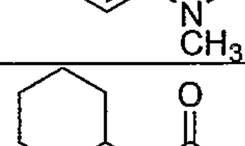
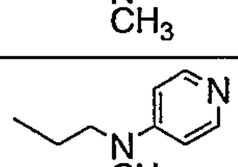
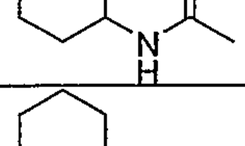
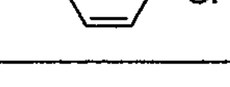
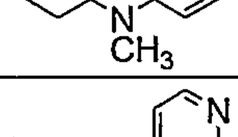
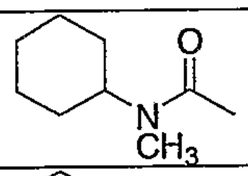
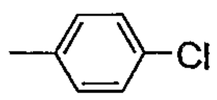
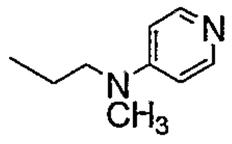
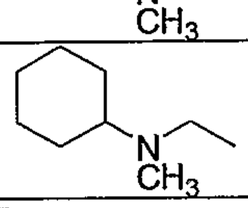
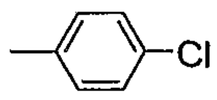
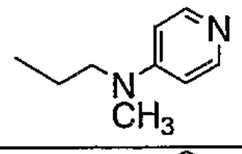
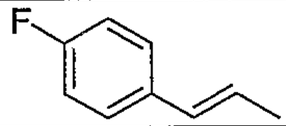
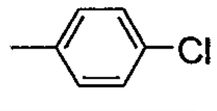
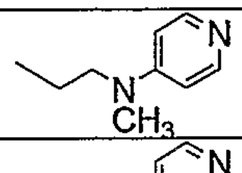
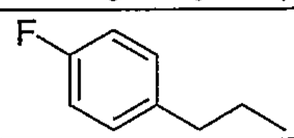
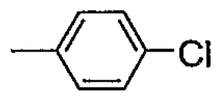
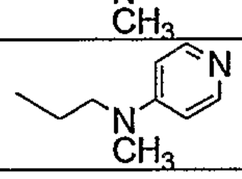
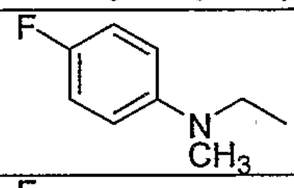
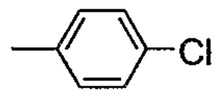
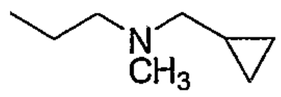
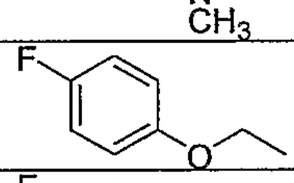
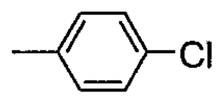
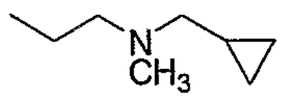
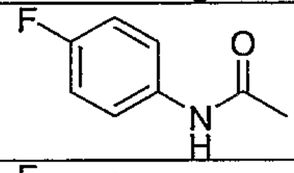
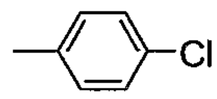
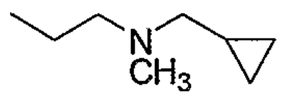
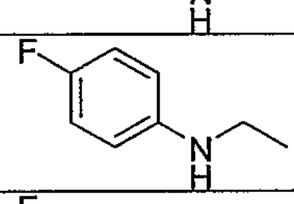
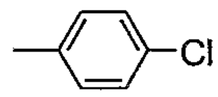
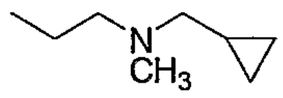
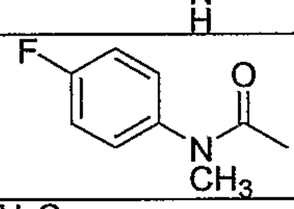
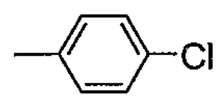
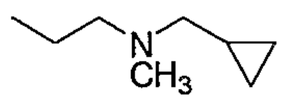
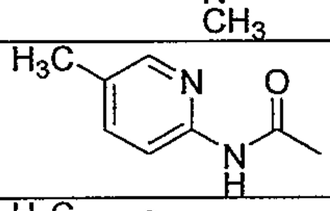
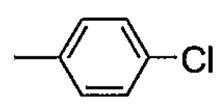
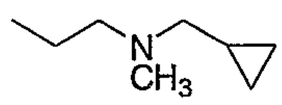
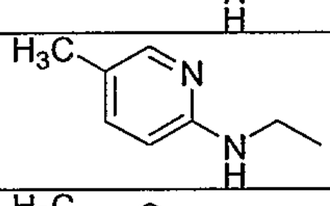
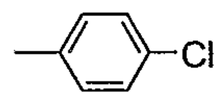
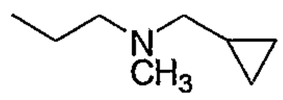
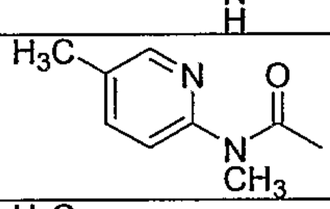
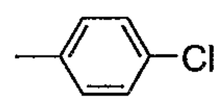
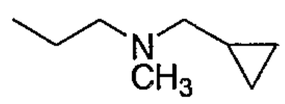
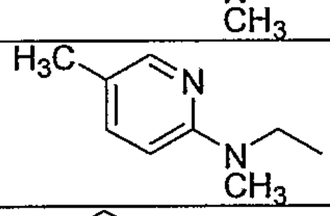
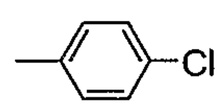
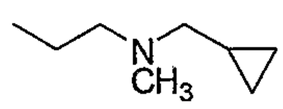
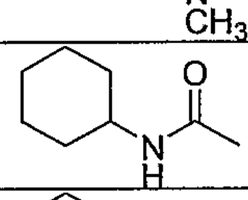
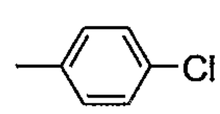
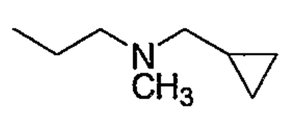
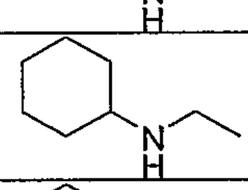
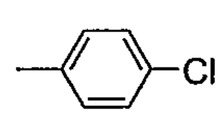
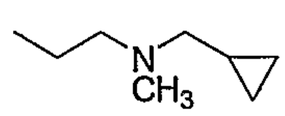
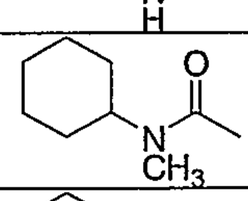
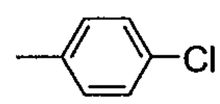
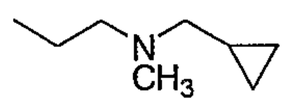
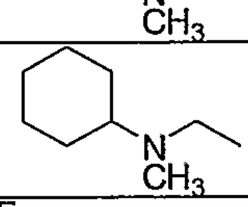
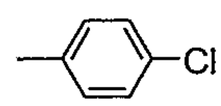
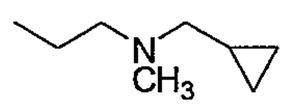
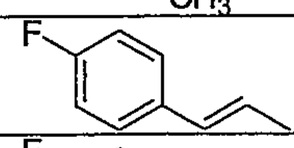
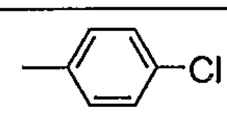
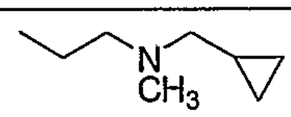
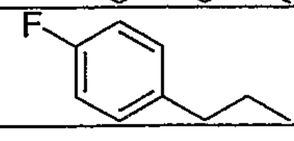
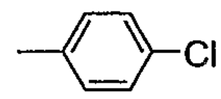
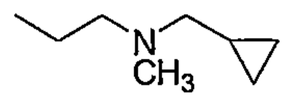
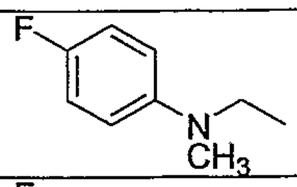
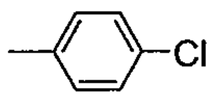
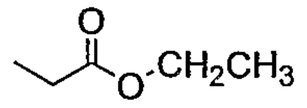
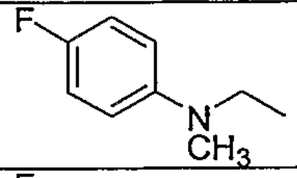
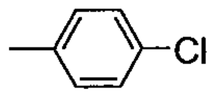
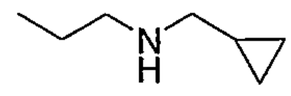
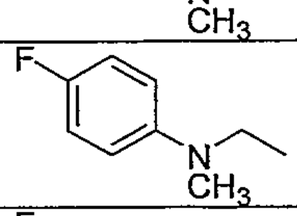
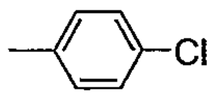
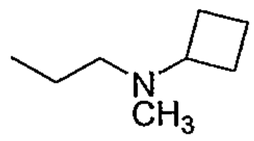
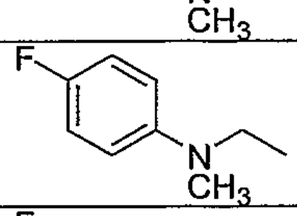
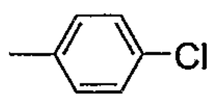
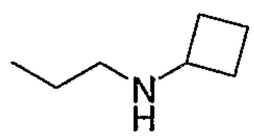
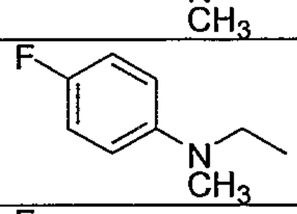
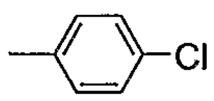
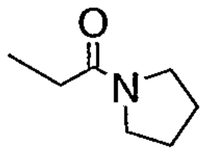
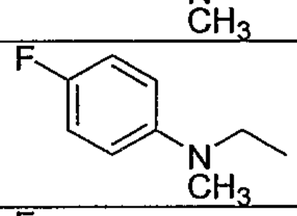
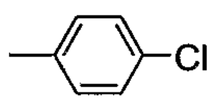
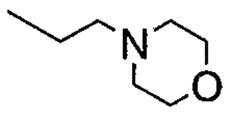
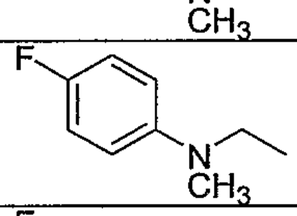
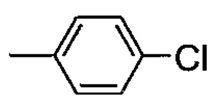
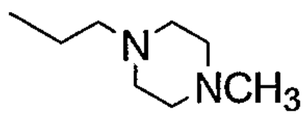
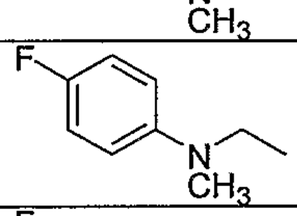
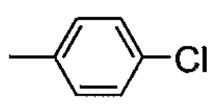
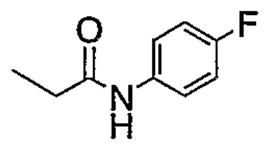
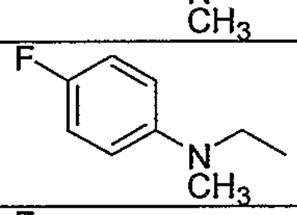
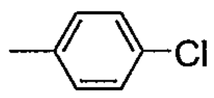
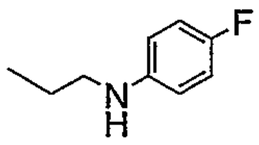
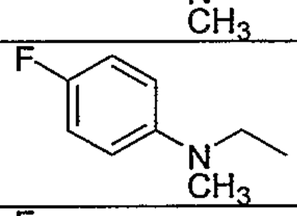
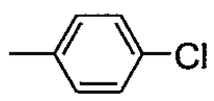
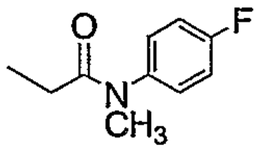
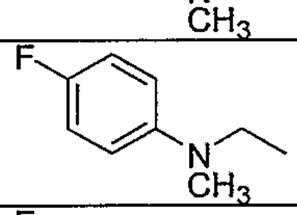
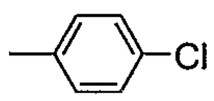
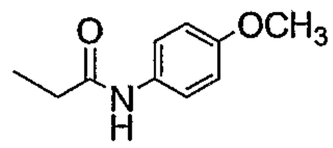
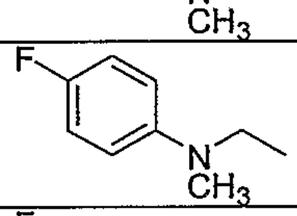
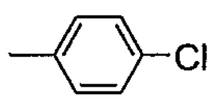
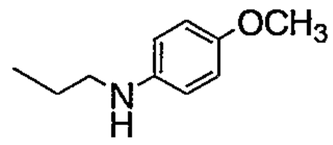
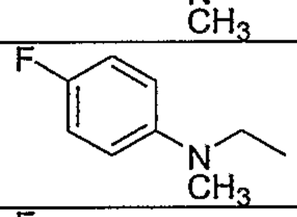
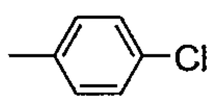
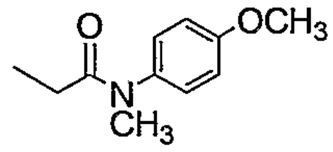
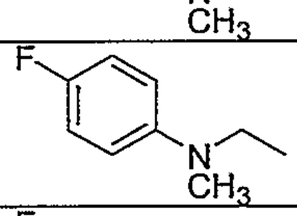
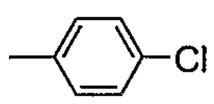
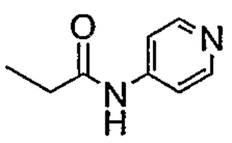
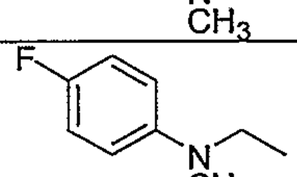
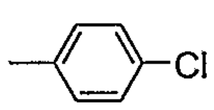
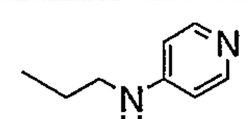
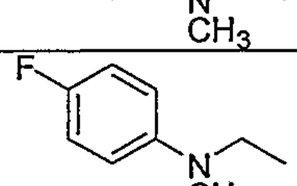
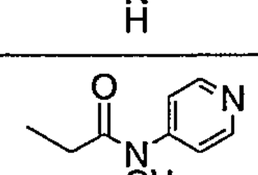
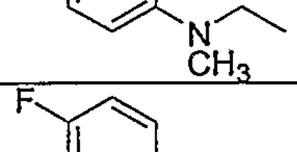
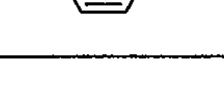
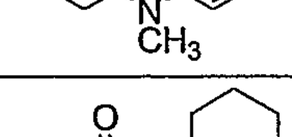
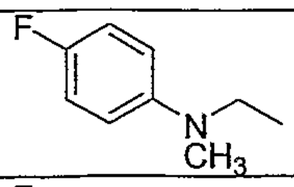
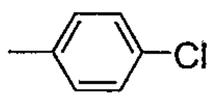
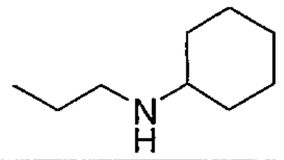
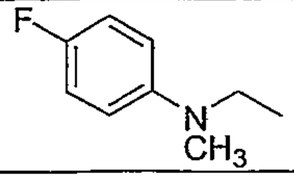
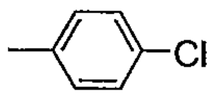
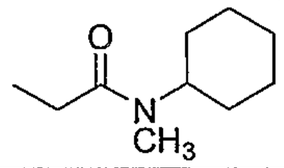
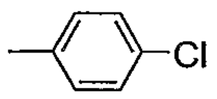
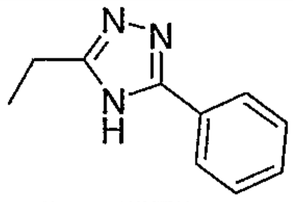
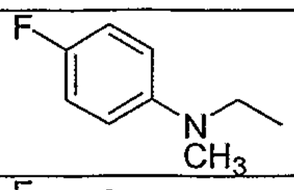
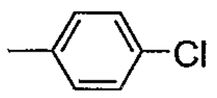
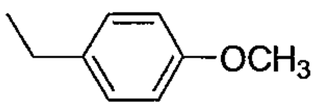
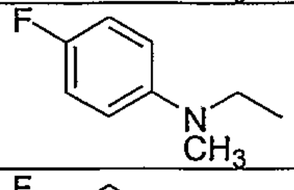
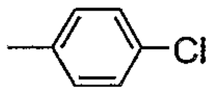
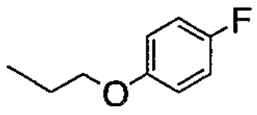
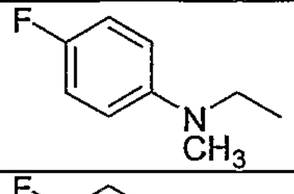
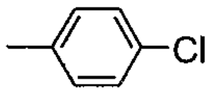
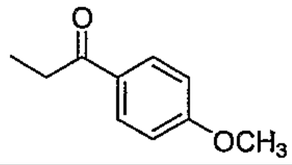
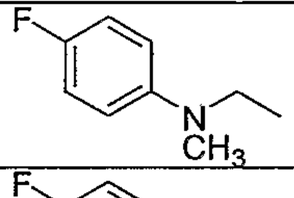
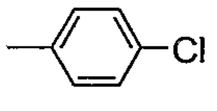
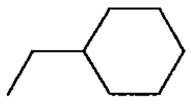
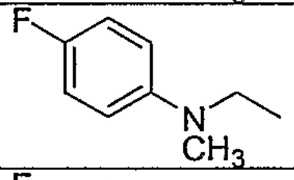
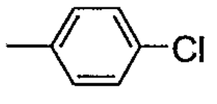
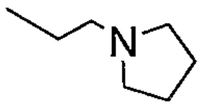
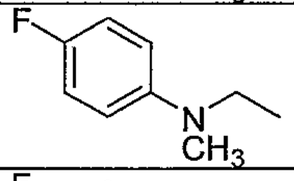
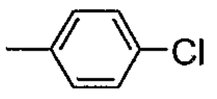
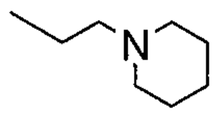
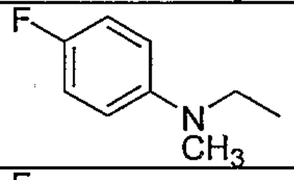
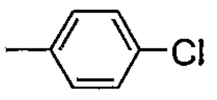
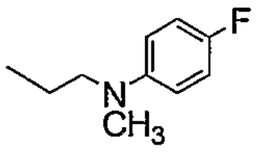
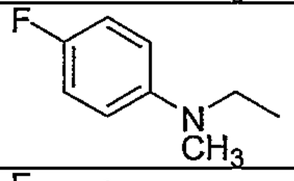
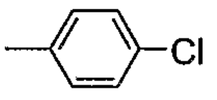
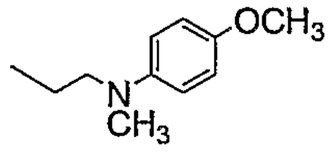
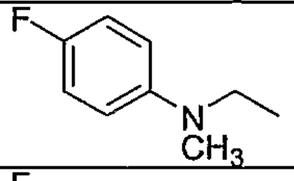
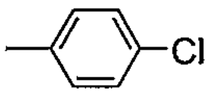
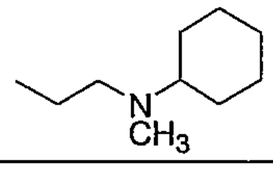
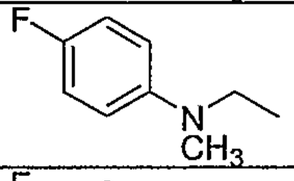
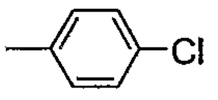
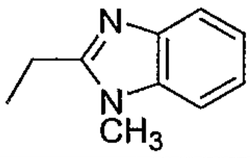
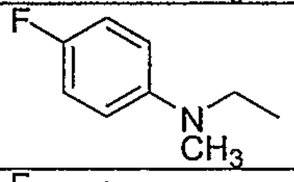
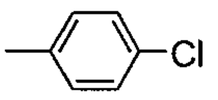
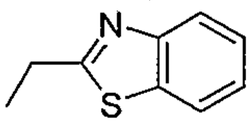
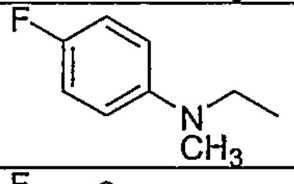
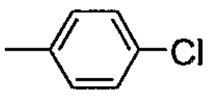
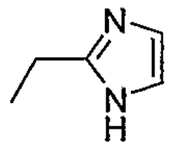
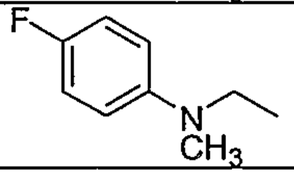
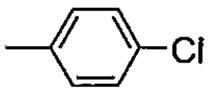
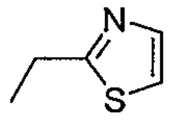
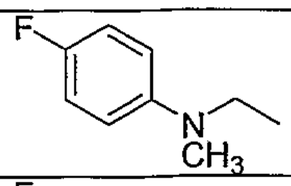
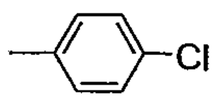
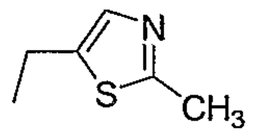
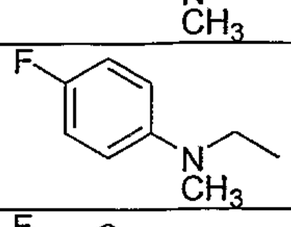
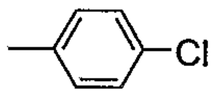
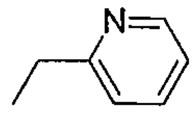
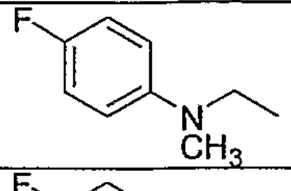
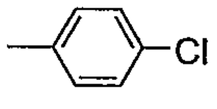
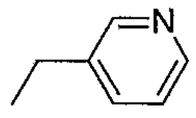
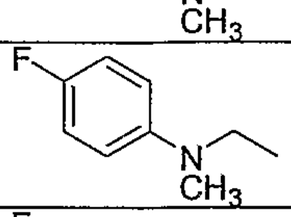
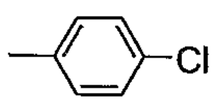
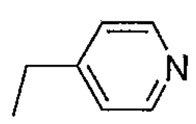
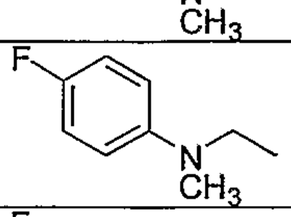
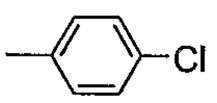
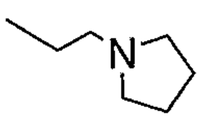
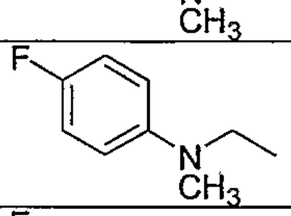
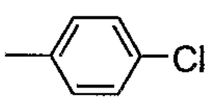
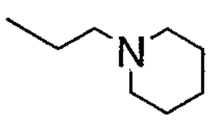
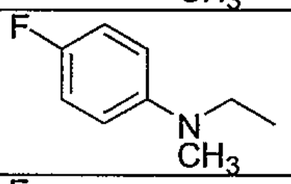
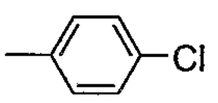
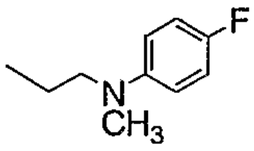
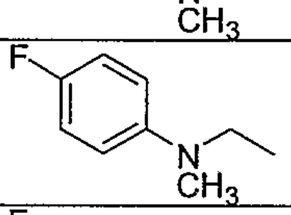
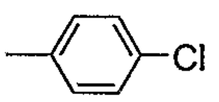
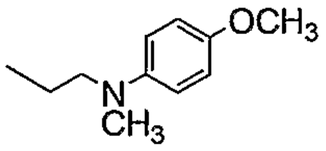
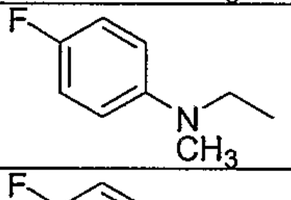
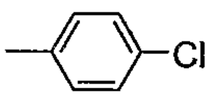
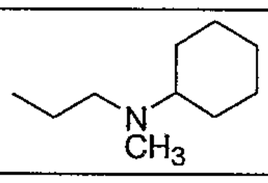
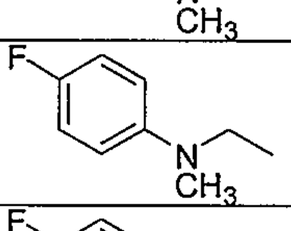
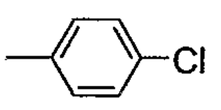
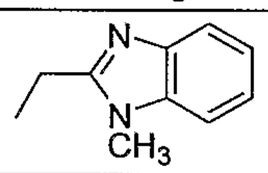
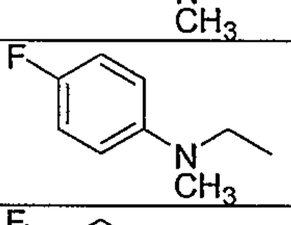
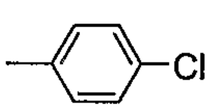
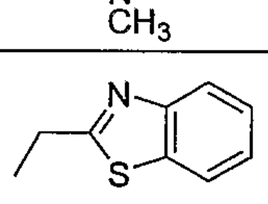
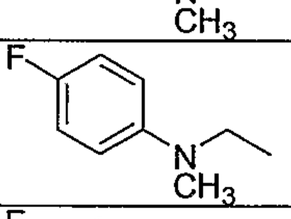
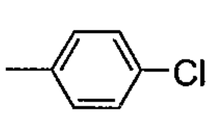
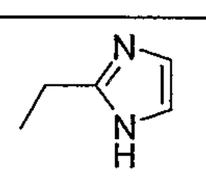
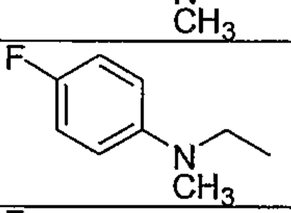
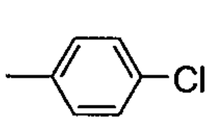
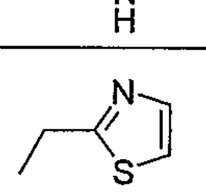
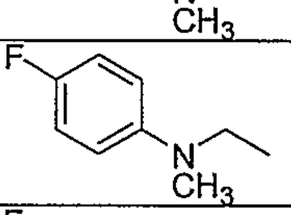
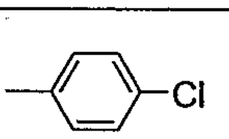
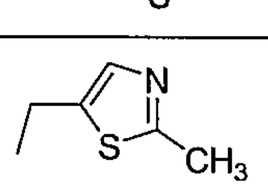
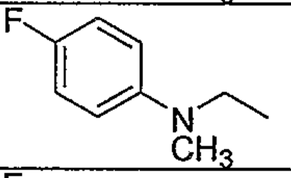
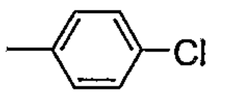
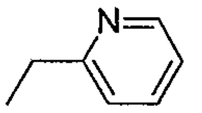
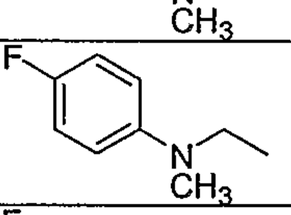
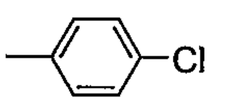
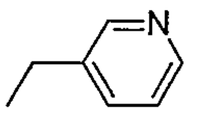
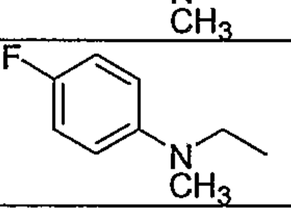
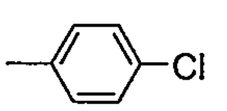
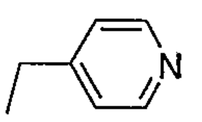
C602			
C603			
C604			
C605			
C606			
C607			
C608			
C609			

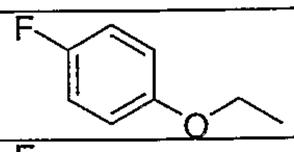
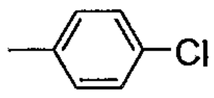
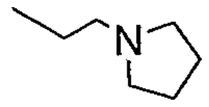
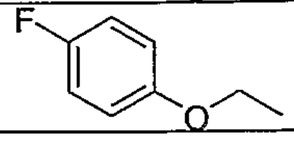
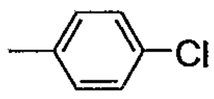
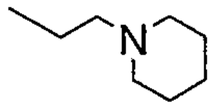
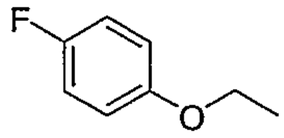
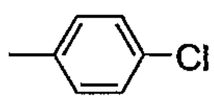
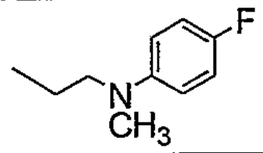
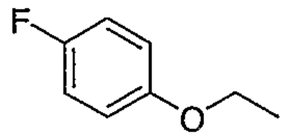
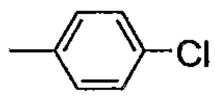
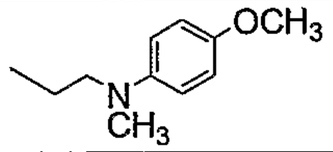
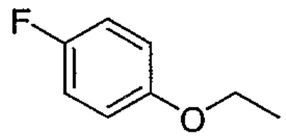
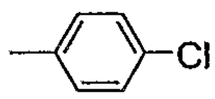
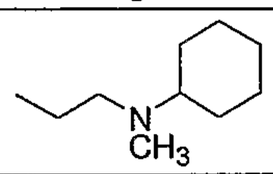
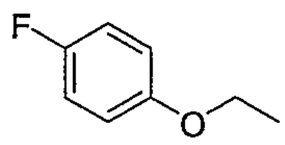
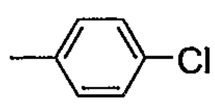
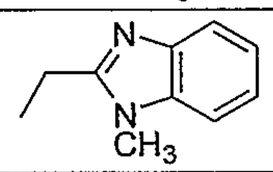
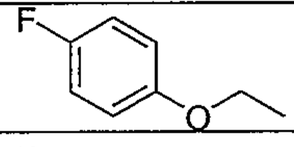
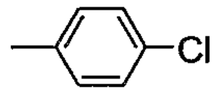
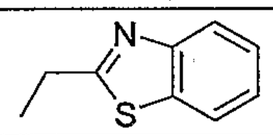
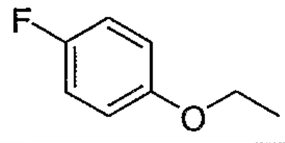
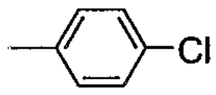
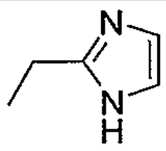
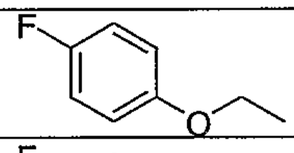
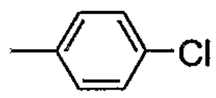
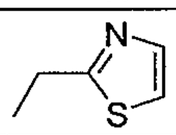
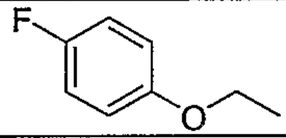
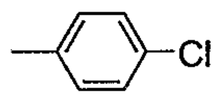
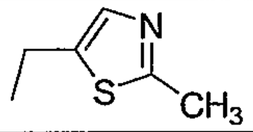
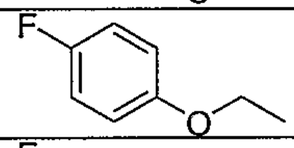
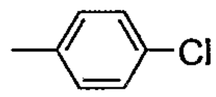
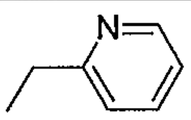
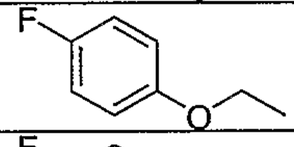
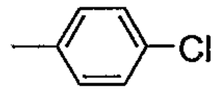
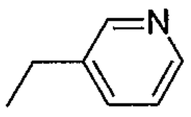
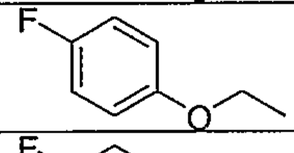
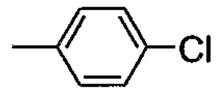
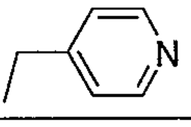
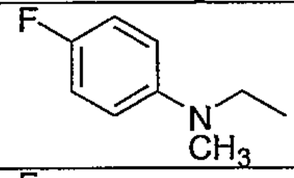
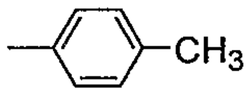
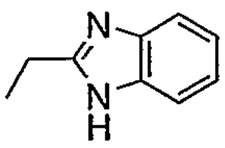
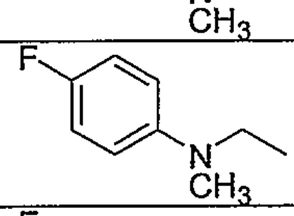
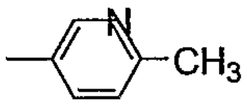
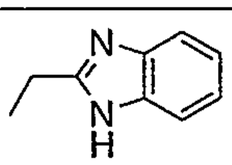
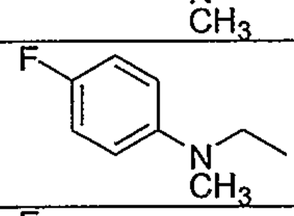
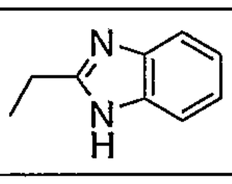
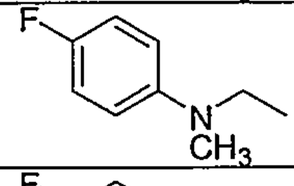
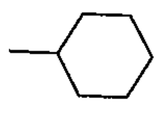
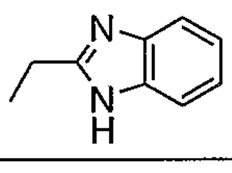
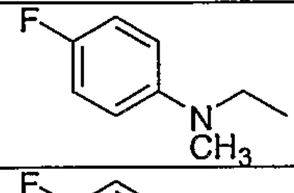
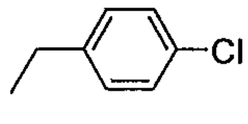
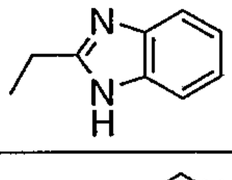
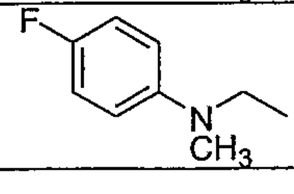
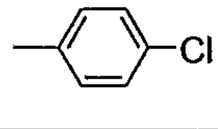
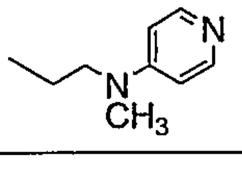
C610			
C611			
C612			
C613			
C614			
C615			
C616			
C617			
C618			
C619			
C620			
C621			
C622			
C623			
C624			
C625			
C626			
C627			

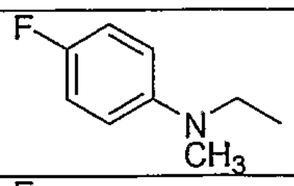
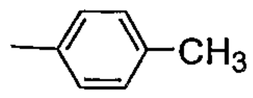
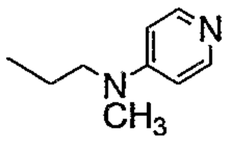
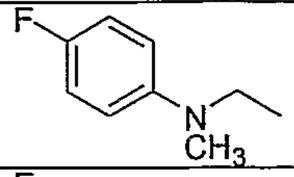
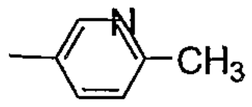
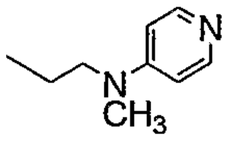
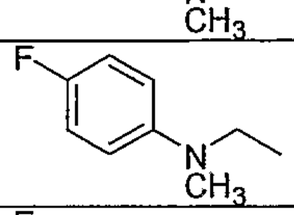
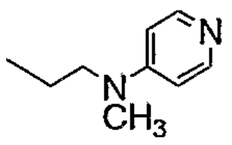
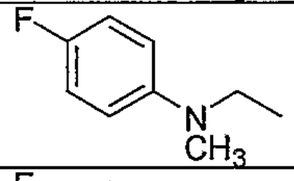
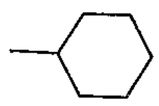
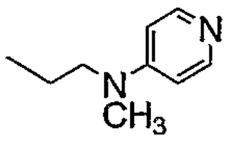
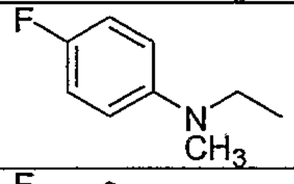
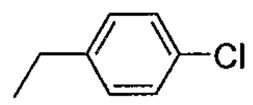
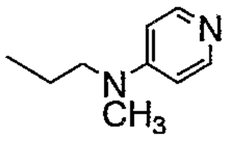
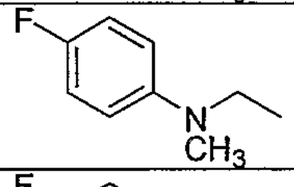
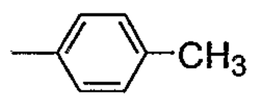
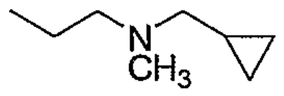
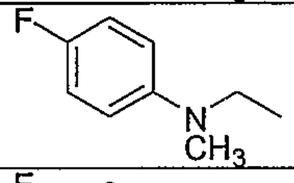
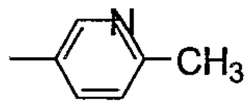
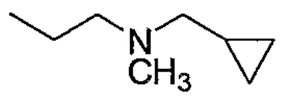
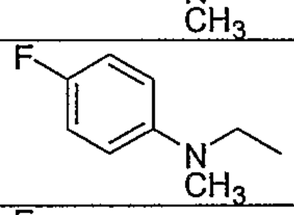
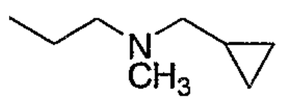
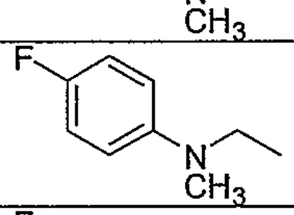
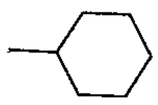
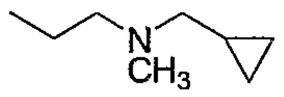
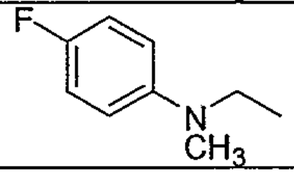
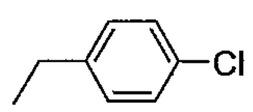
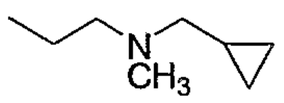
C628			
C629			
C630			
C631			
C632			
C633			
C634			
C635			
C636			
C637			
C638			
C639			
C640			
C641			
C642			
C643			
C644			
C645			
C646			

C647			
C648			
C649			
C650			
C651			
C652			
C653			
C654			
C655			
C656			
C657			
C658			
C659			
C660			
C661			
C662			
C663			

C664			
C665			
C666			
C667			
C668			
C669			
C670			
C671			
C672			
C673			
C674			
C675			
C676			
C677			
C678			
C679			

C680			
C681			
C682			
C683			
C684			
C685			
C686			
C687			
C688			
C689			
C690			
C691			
C692			
C693			
C694			
C695			
C696			

C697			
C698			
C699			
C700			
C701			
C702			
C703			
C704			
C705			
C706			
C707			
C708			
C709			
C710			
C711			
C712		CH_3	
C713			
C714			
C715			

C716			
C717			
C718		CH_3	
C719			
C720			
C721			
C722			
C723		CH_3	
C724			
C725			

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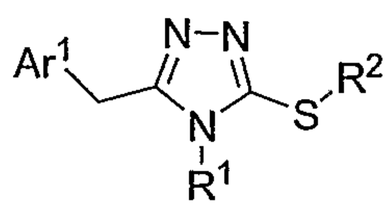

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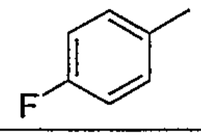
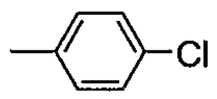
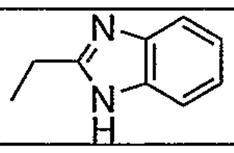
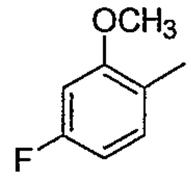
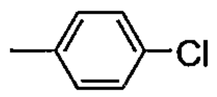
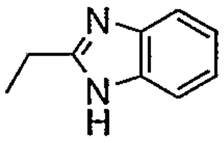
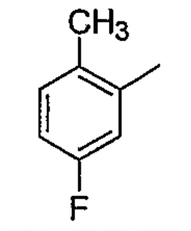
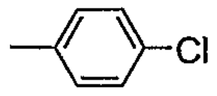
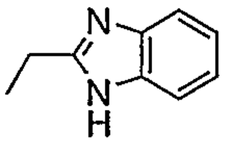
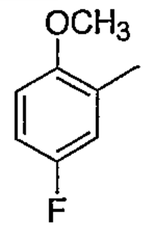
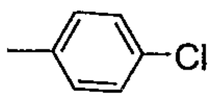
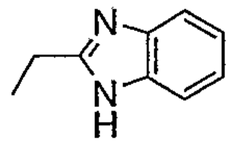
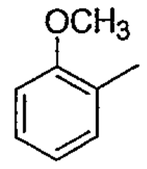
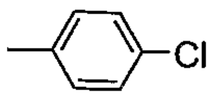
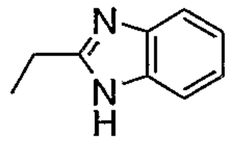
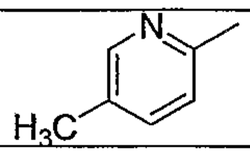
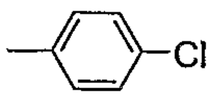
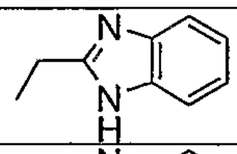
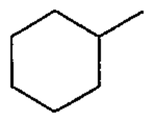
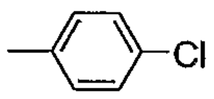
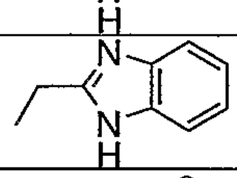
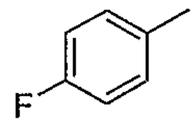
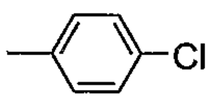
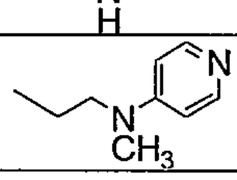
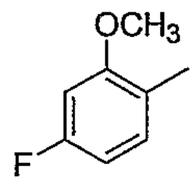
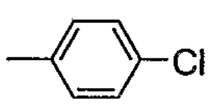
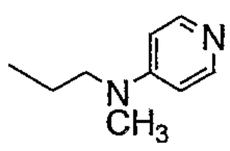
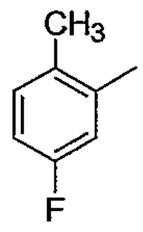
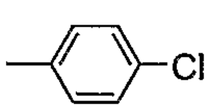
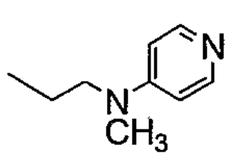
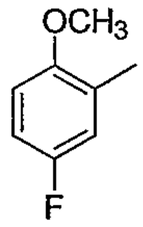
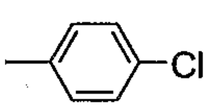
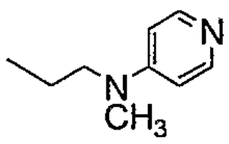
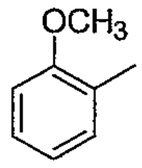
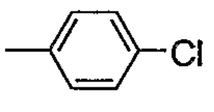
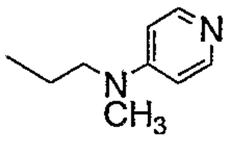
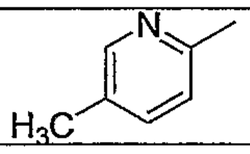
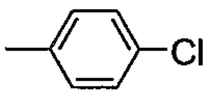
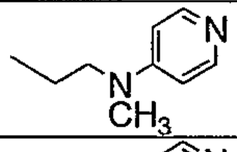
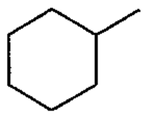
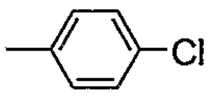
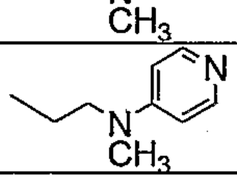
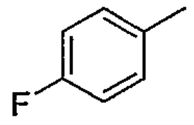
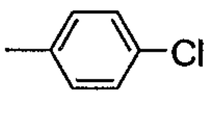
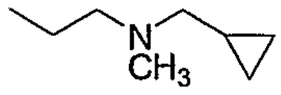
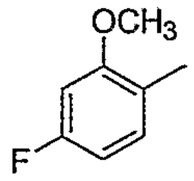
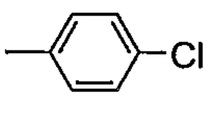
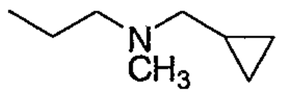
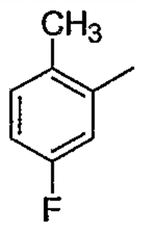
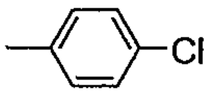
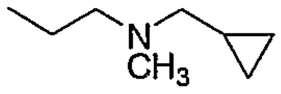
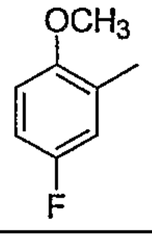
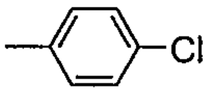
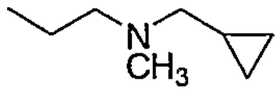
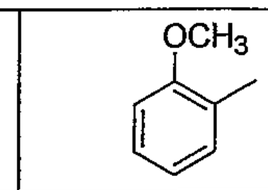
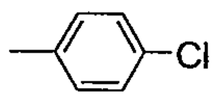
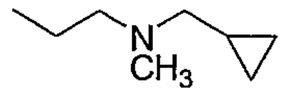
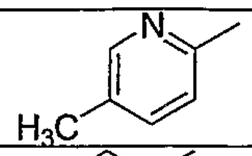
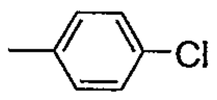
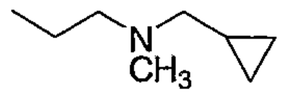
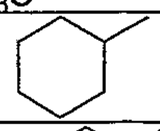
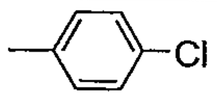
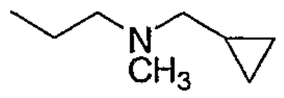
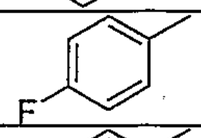
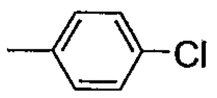
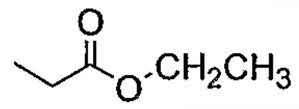
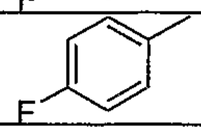
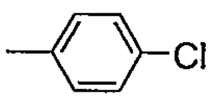
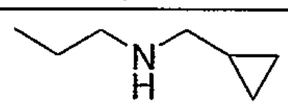
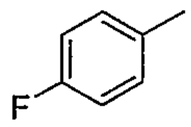
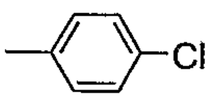
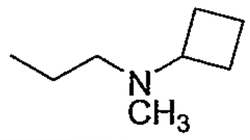
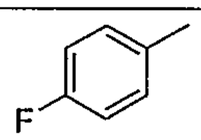
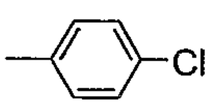
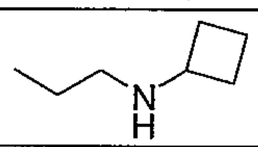
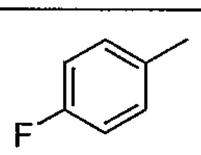
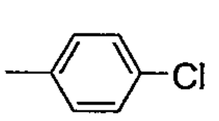
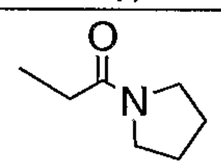
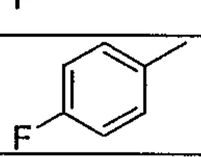
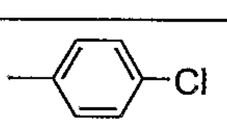
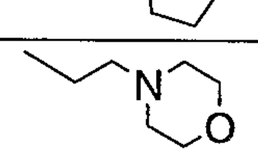
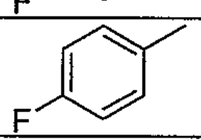
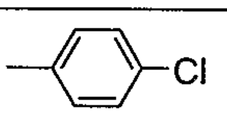
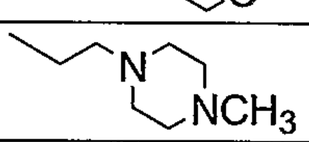
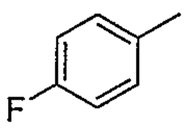
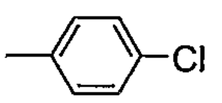
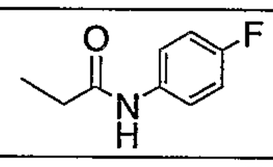
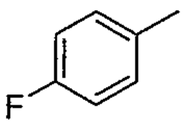
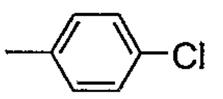
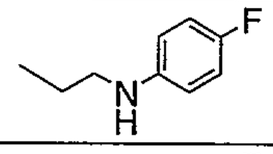
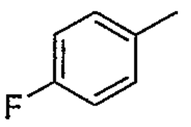
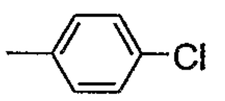
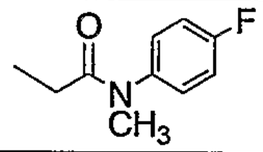
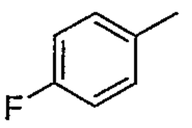
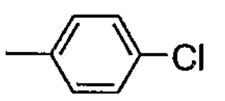
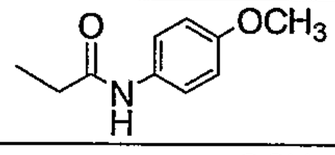
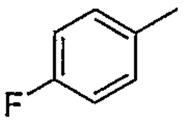
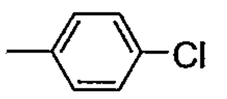
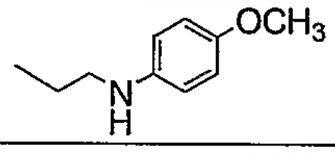
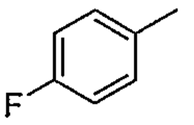
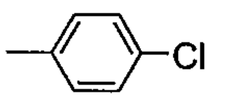
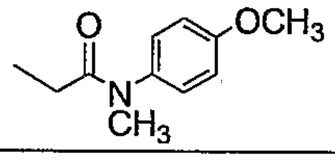
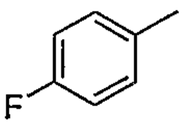
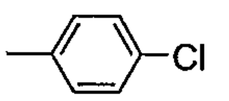
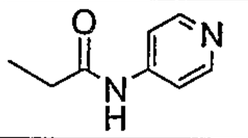
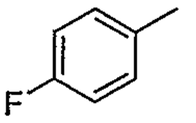
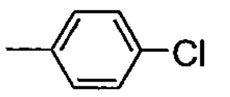
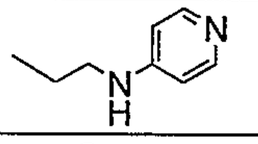
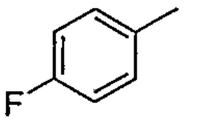
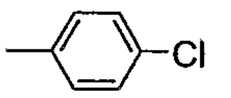
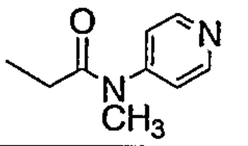
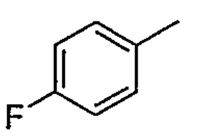
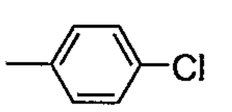
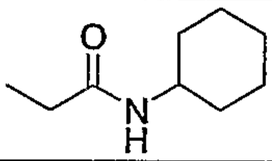
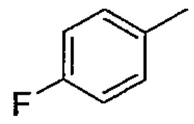
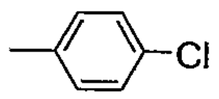
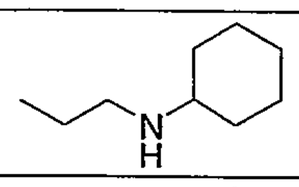
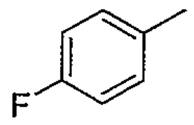
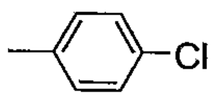
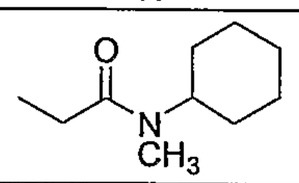
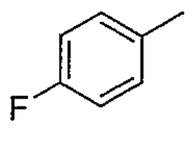
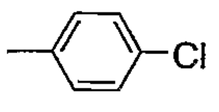
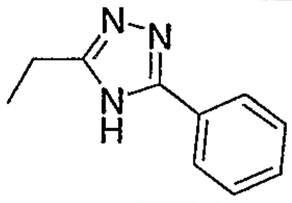
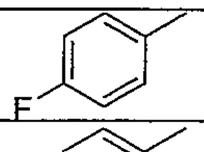
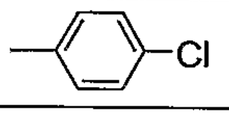
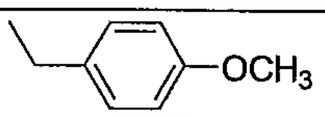
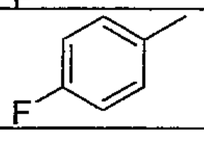
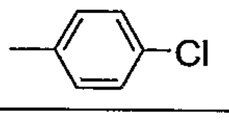
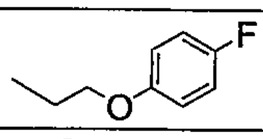
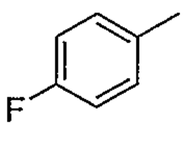
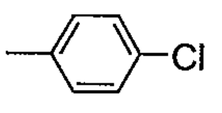
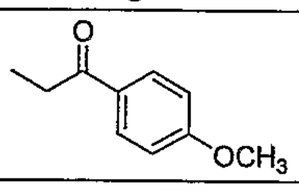
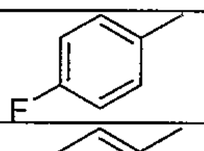
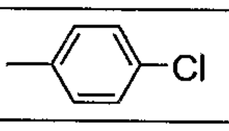
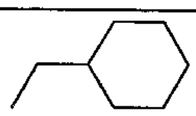
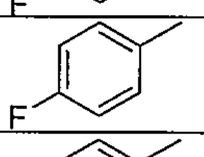
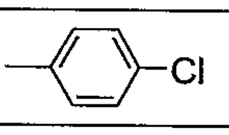
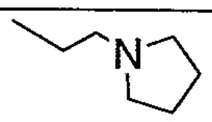
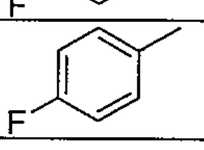
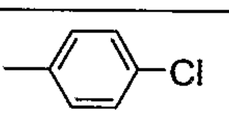
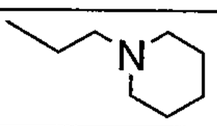
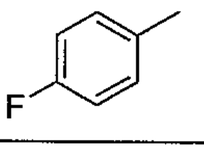
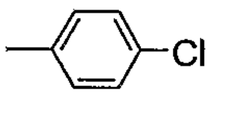
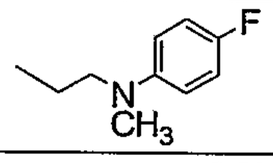
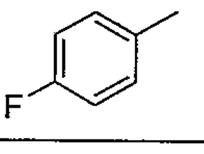
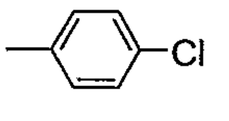
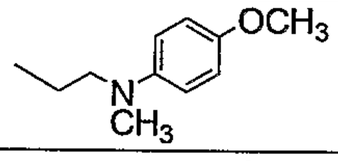
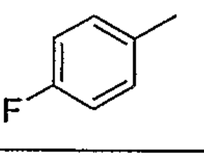
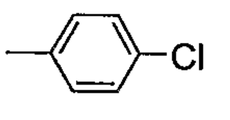
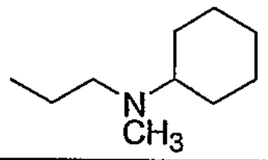
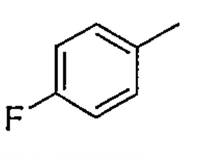
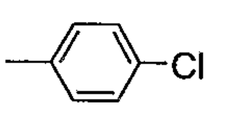
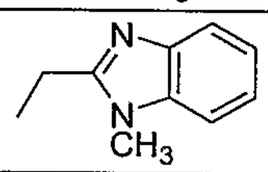
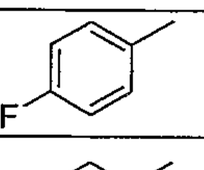
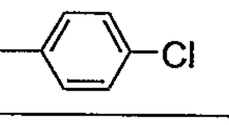
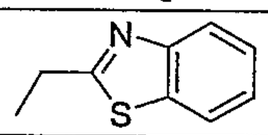
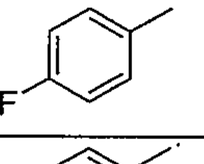
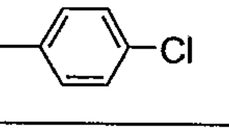
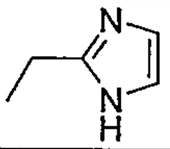
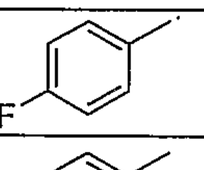
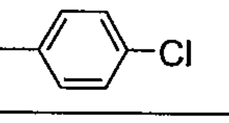
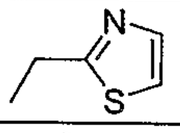
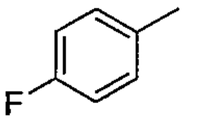
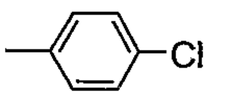
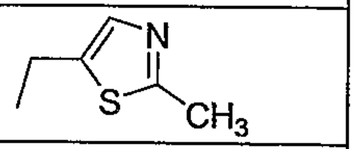
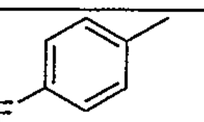
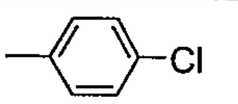
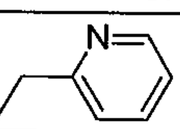
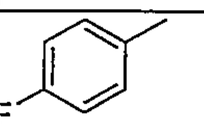
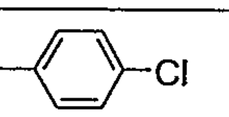
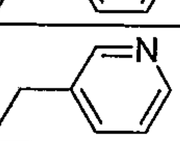
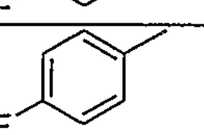
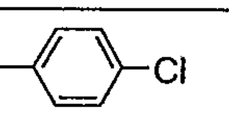
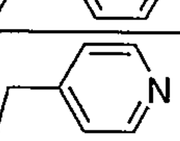
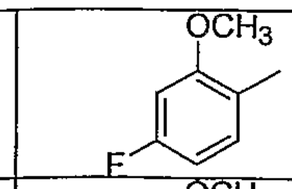
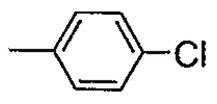
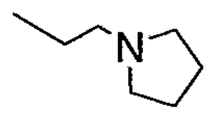
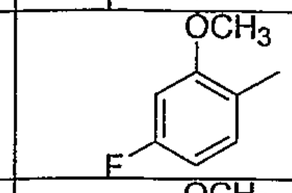
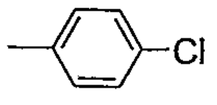
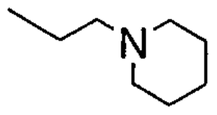
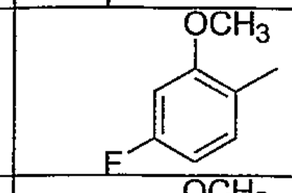
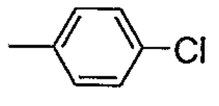
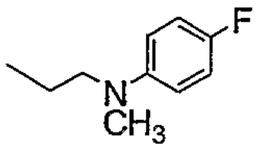
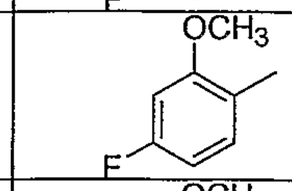
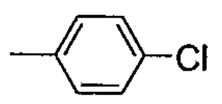
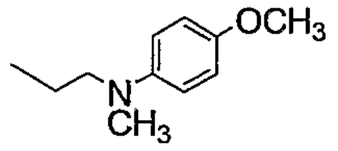
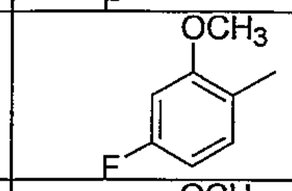
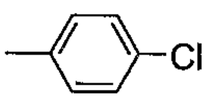
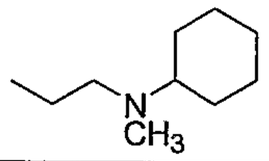
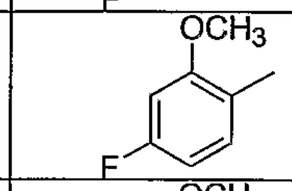
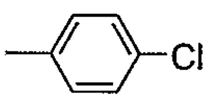
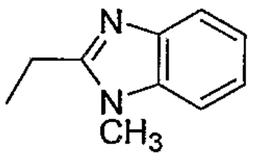
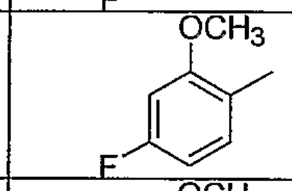
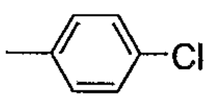
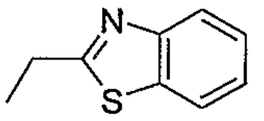
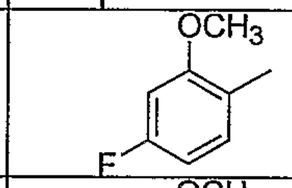
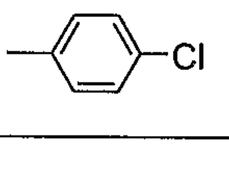
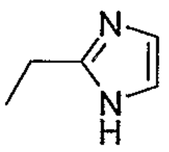
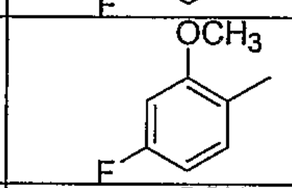
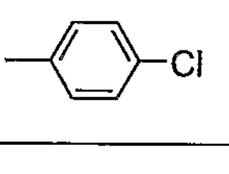
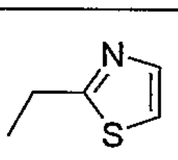
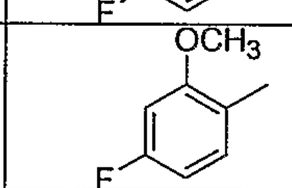
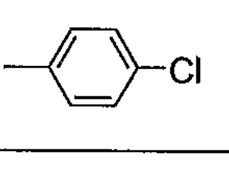
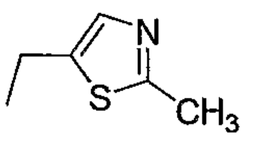
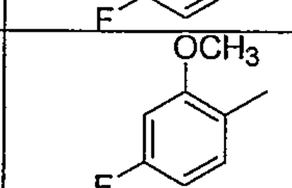
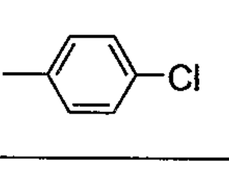
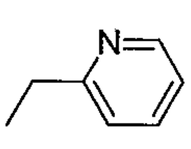
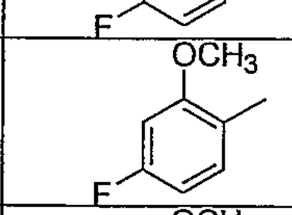
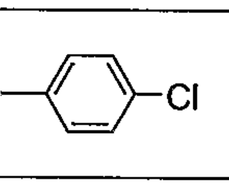
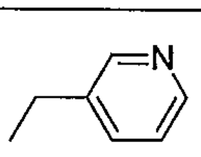
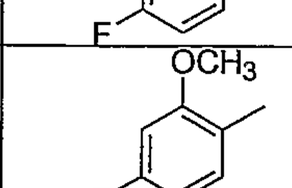
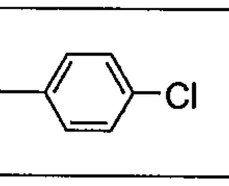
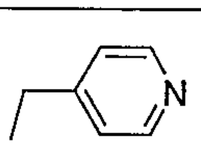
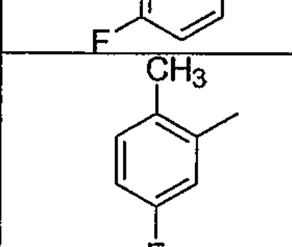
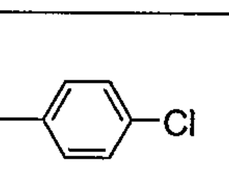
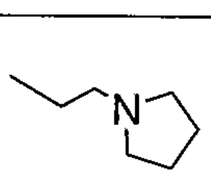
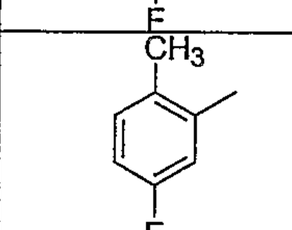
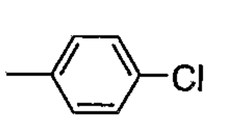
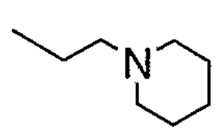
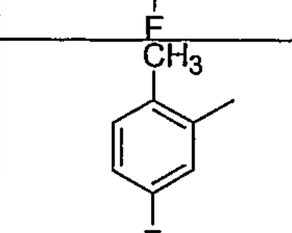
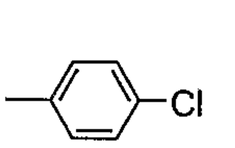
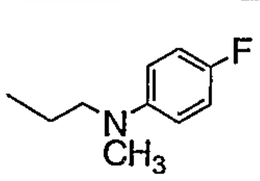
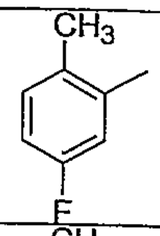
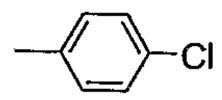
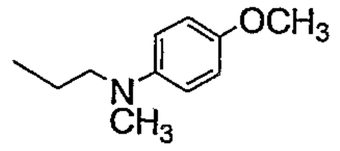
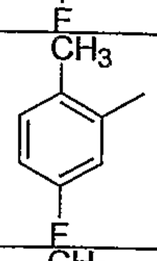
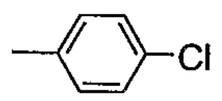
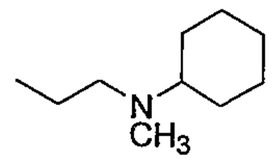
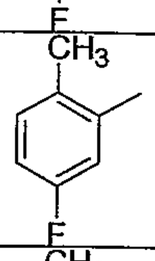
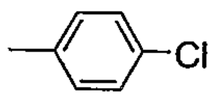
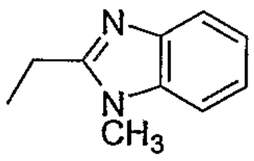
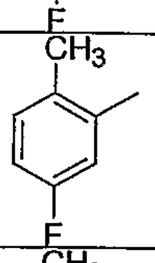
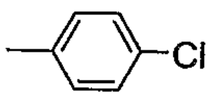
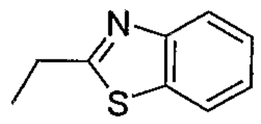
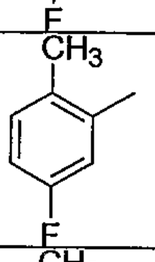
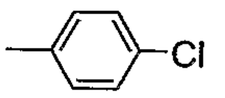
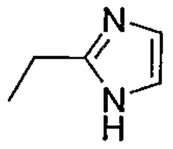
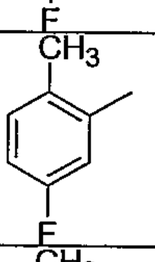
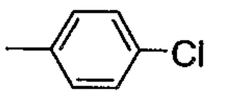
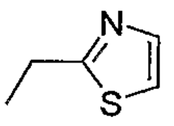
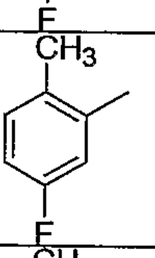
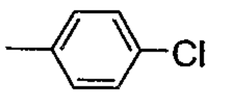
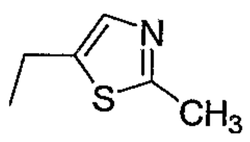
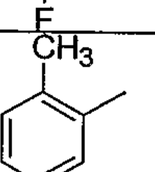
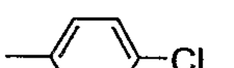
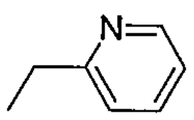
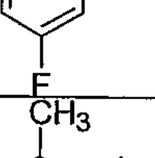
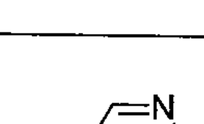
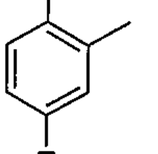
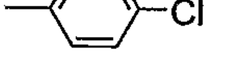
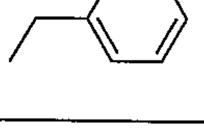
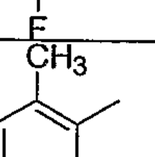
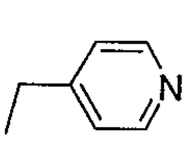
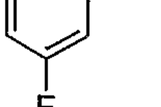
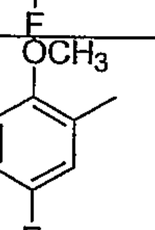
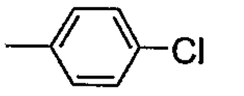
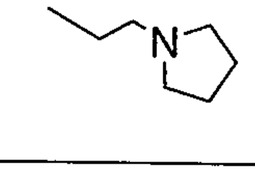
C726			
C727			
C728			

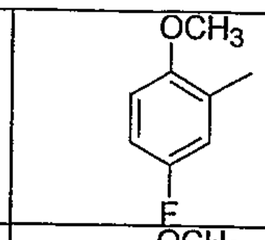
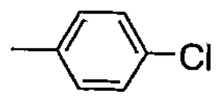
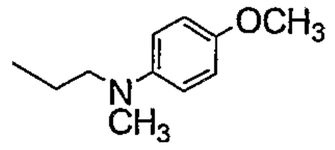
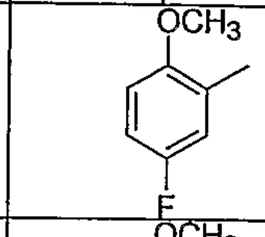
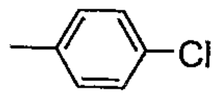
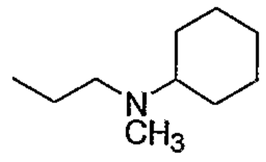
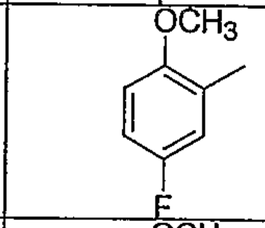
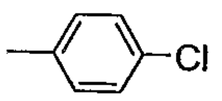
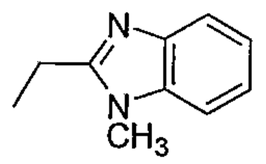
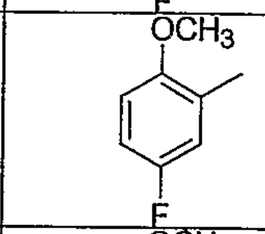
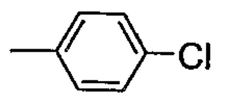
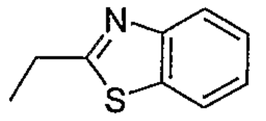
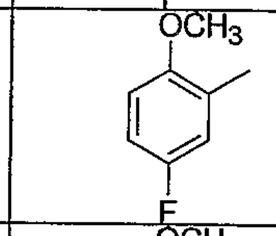
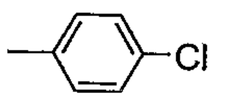
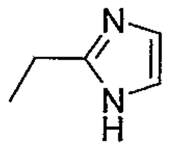
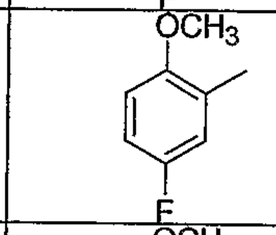
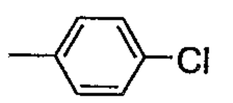
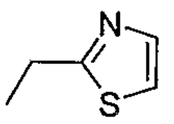
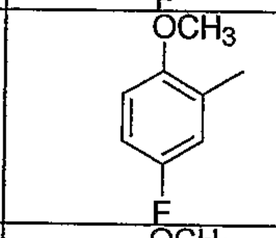
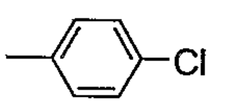
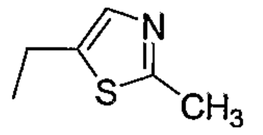
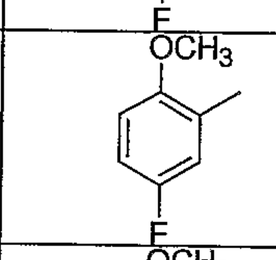
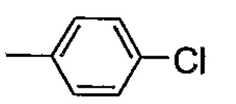
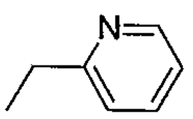
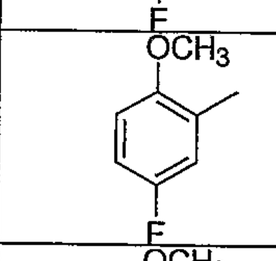
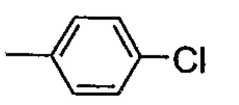
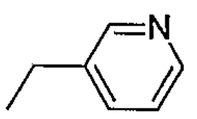
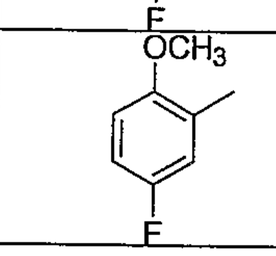
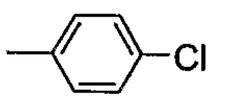
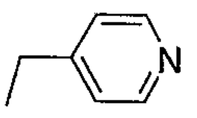
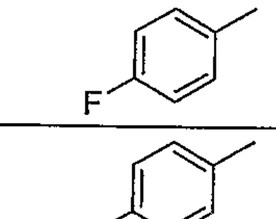
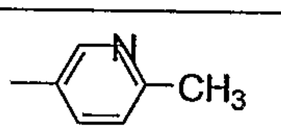
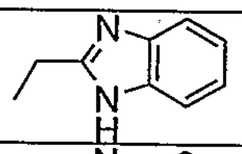
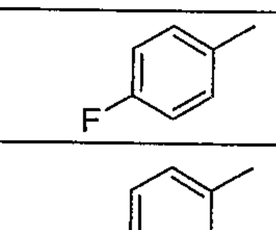
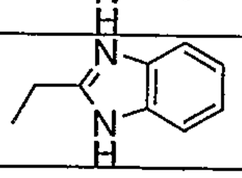
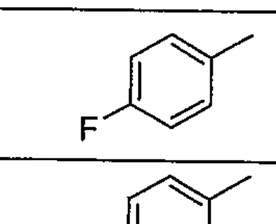
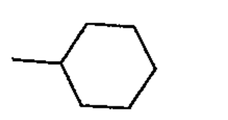
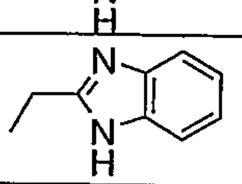
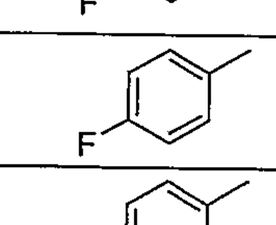
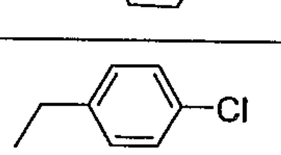
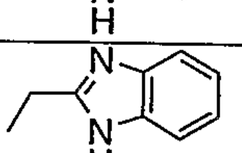
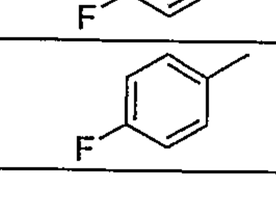
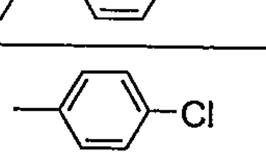
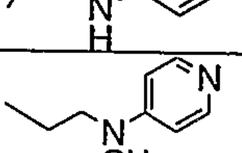
C729			
C730			
C731			
C732			
C733			
C734			
C735			
C736			
C737			
C738			
C739			
C740			
C741			
C742			
C743			

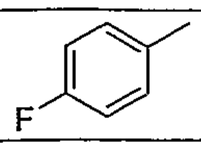
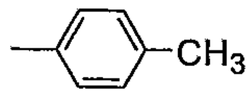
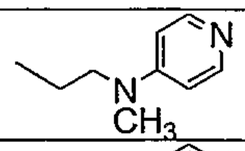
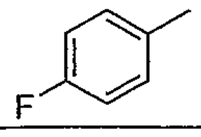
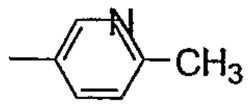
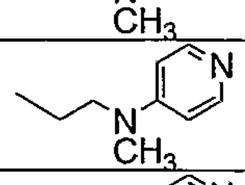
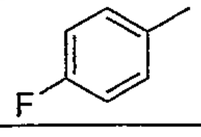
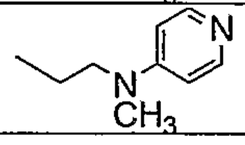
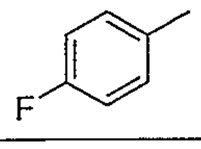
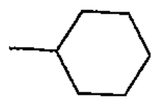
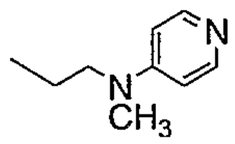
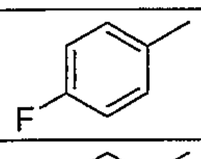
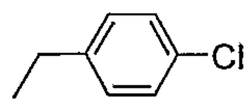
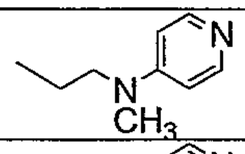
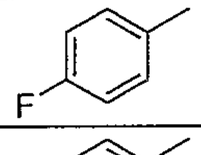
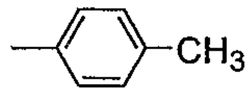
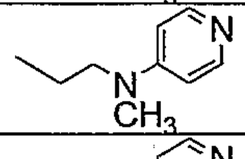
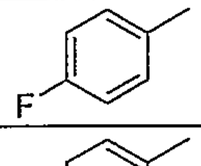
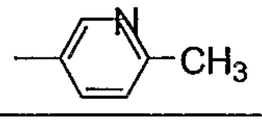
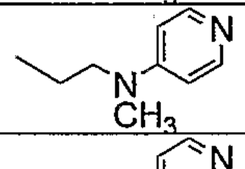
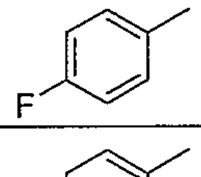
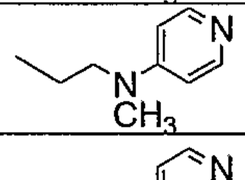
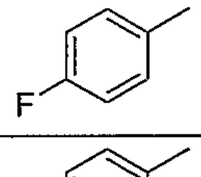
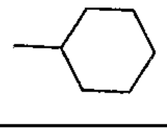
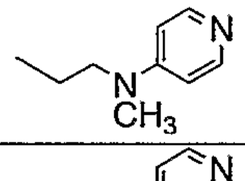
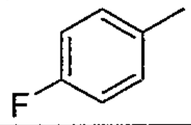
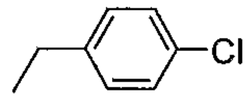
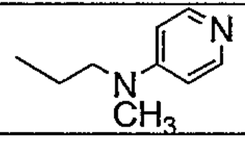
C744			
C745			
C746			
C747			
C748			
C749			
C750			
C751			
C752			
C753			
C754			
C755			
C756			
C757			
C758			
C759			
C760			
C761			
C762			
C763			

C764			
C765			
C766			
C767			
C768			
C769			
C770			
C771			
C772			
C773			
C774			
C775			
C776			
C777			
C778			
C779			
C780			
C781			
C782			
C783			

C784			
C785			
C786			
C787			
C788			
C789			
C790			
C791			
C792			
C793			
C794			
C795			
C796			
C797			
C798			
C799			

C800			
C801			
C802			
C803			
C804			
C805			
C806			
C807			
C808			
C809			
C810			
C811			
C812			

C813			
C814			
C815			
C816			
C817			
C818			
C819			
C820			
C821			
C822			
C823			
C824		CH_3	
C825			
C826			
C827			

C828			
C829			
C830		CH_3	
C831			
C832			
C833			
C834			
C835		CH_3	
C836			
C837			

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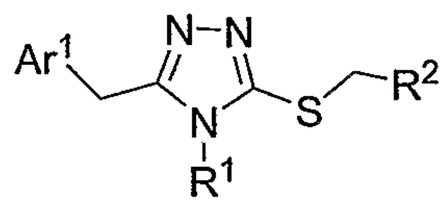

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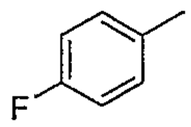
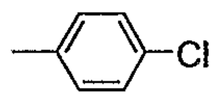
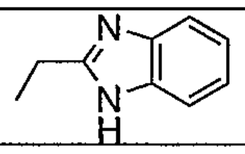
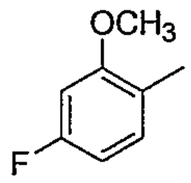
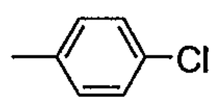
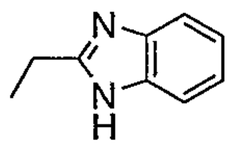
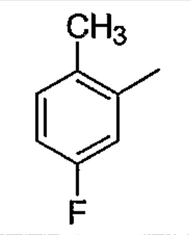
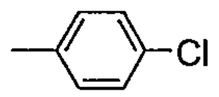
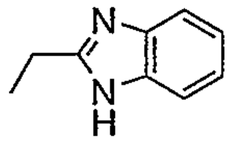
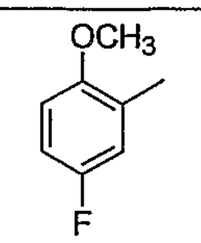
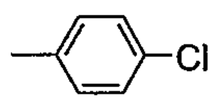
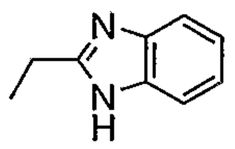
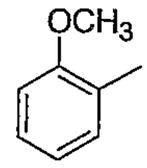
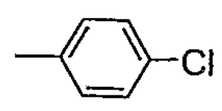
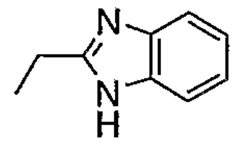
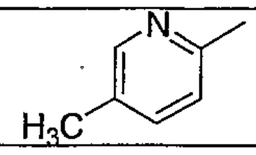
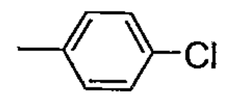
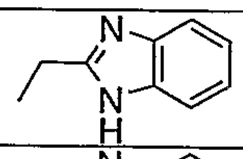
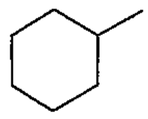
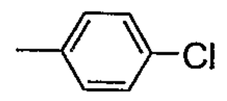
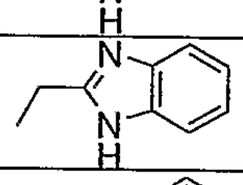
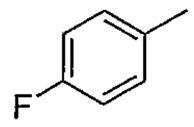
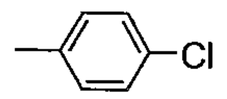
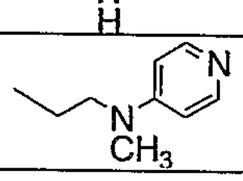
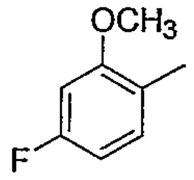
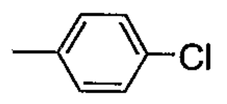
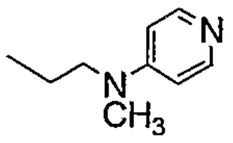
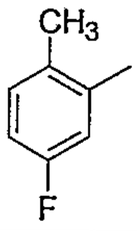
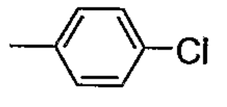
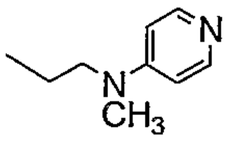
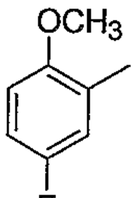
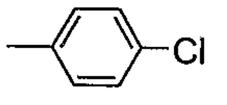
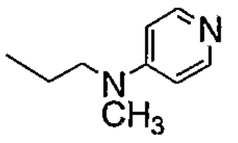
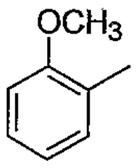
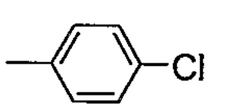
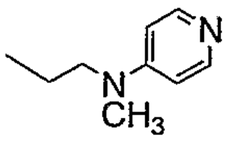
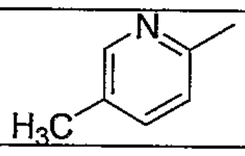
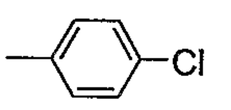
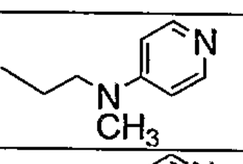
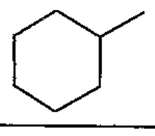
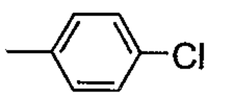
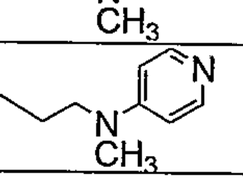
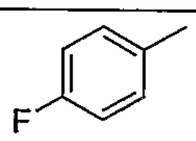
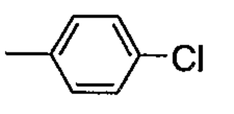
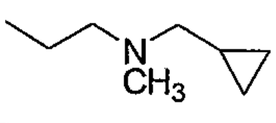
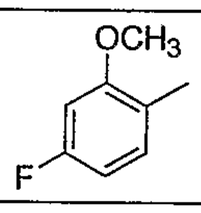
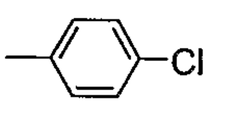
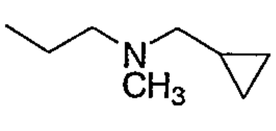
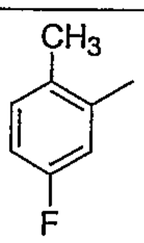
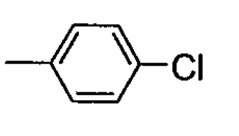
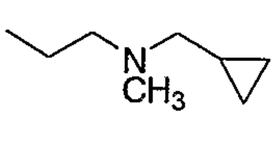
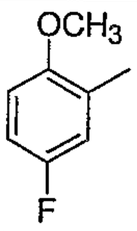
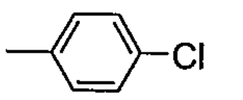
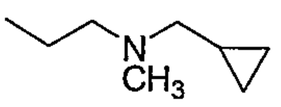
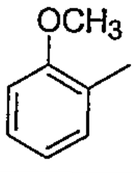
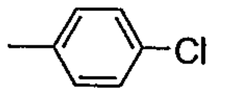
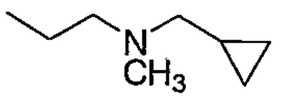
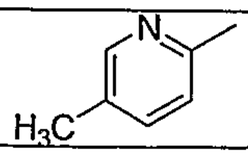
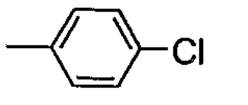
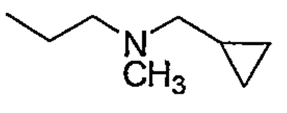
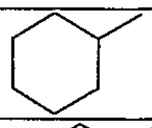
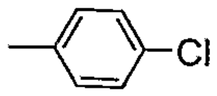
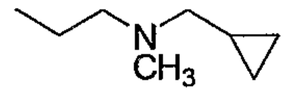
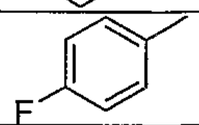
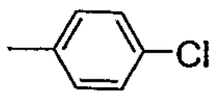
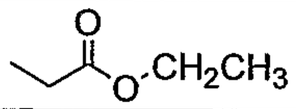
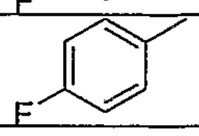
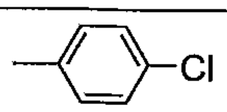
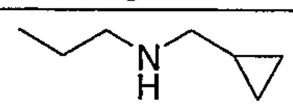
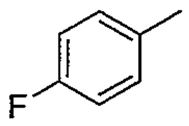
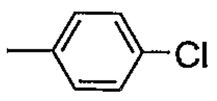
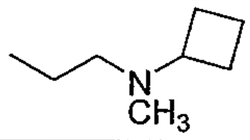
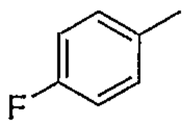
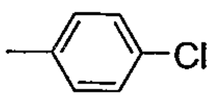
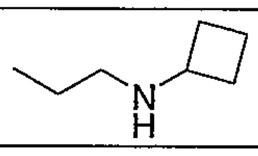
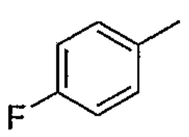
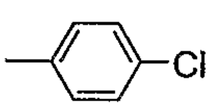
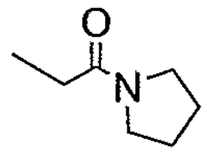
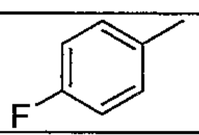
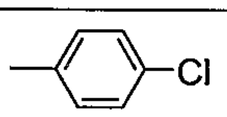
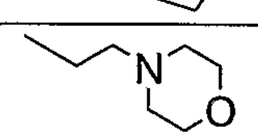
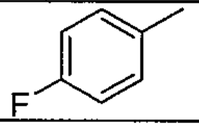
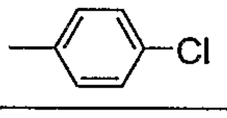
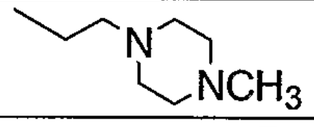
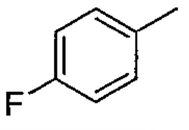
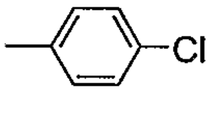
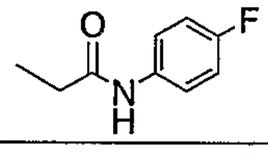
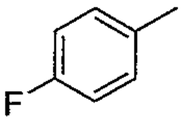
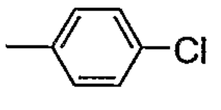
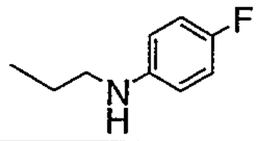
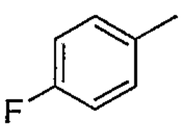
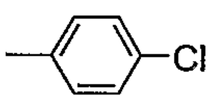
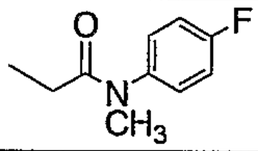
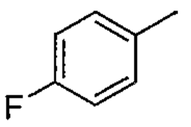
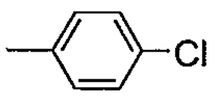
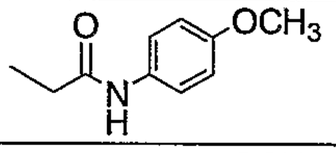
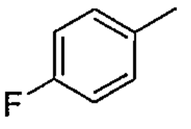
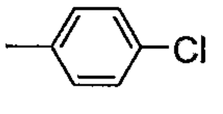
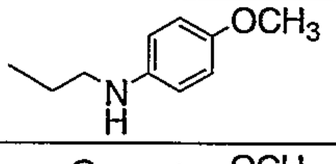
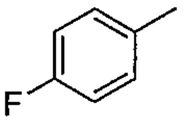
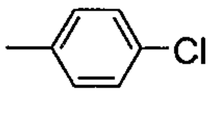
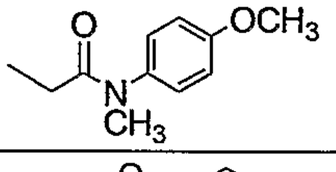
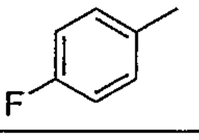
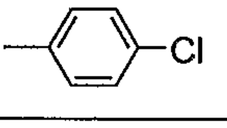
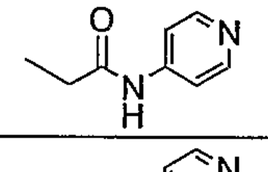
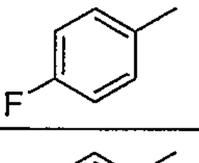
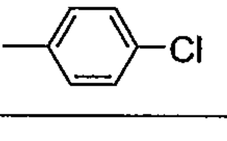
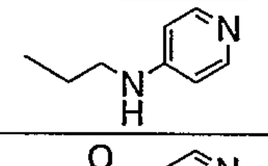
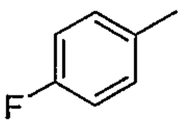
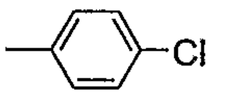
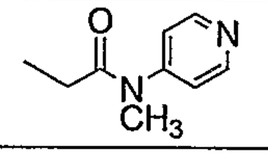
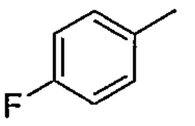
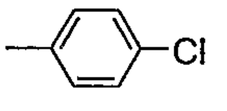
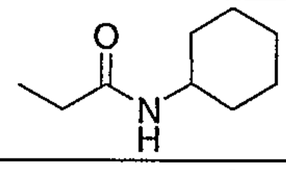
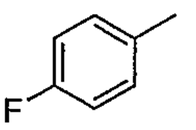
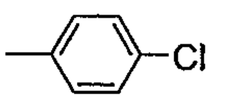
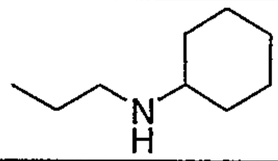
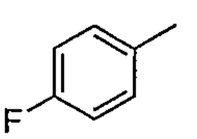
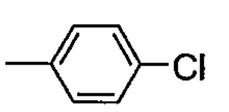
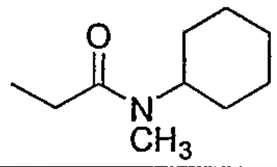
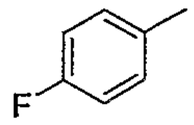
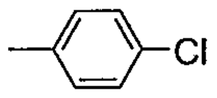
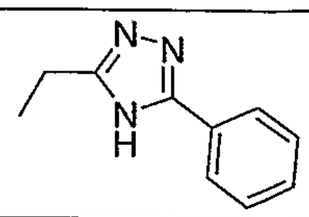
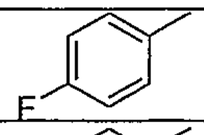
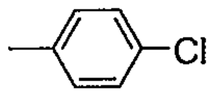
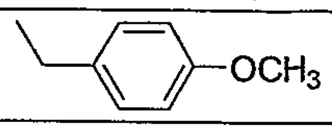
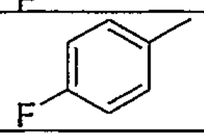
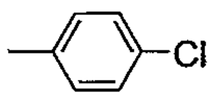
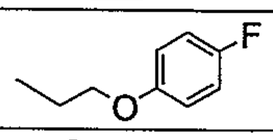
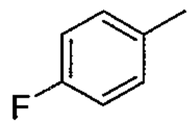
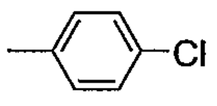
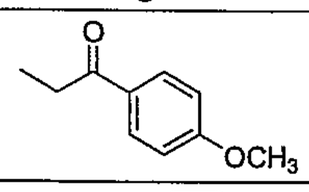
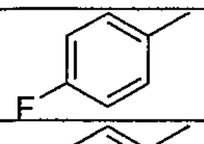
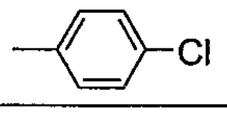
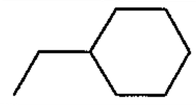
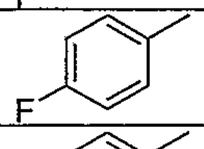
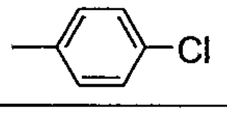
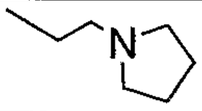
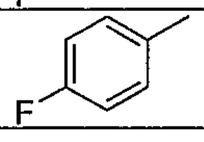
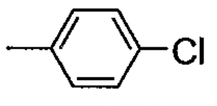
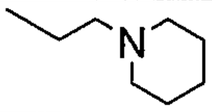
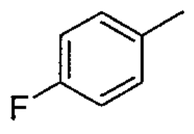
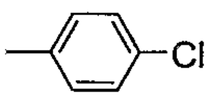
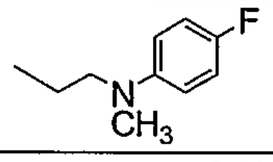
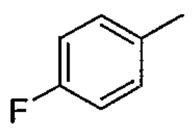
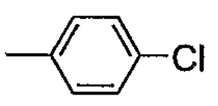
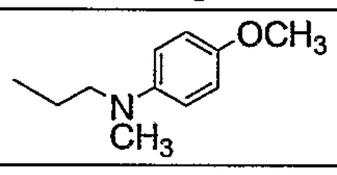
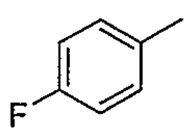
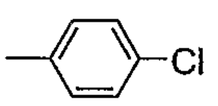
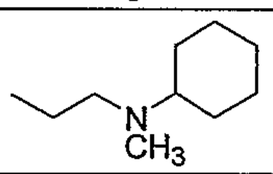
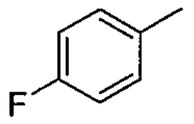
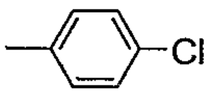
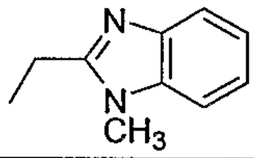
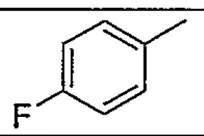
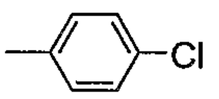
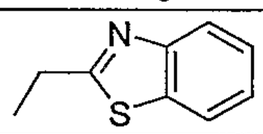
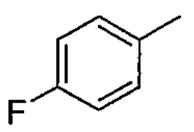
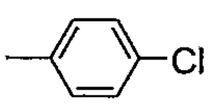
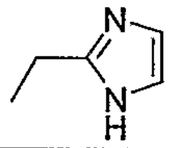
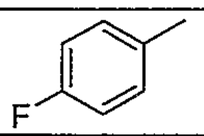
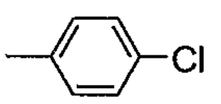
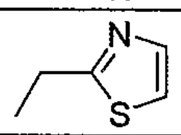
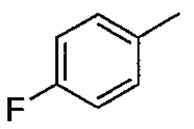
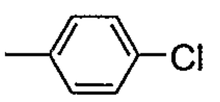
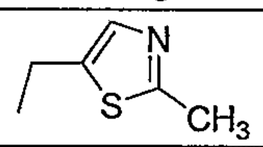
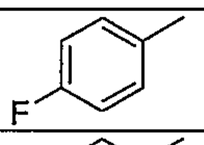
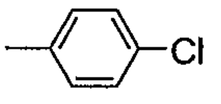
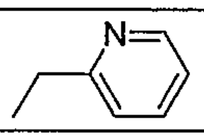
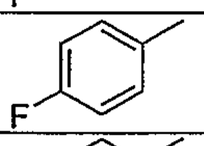
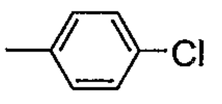
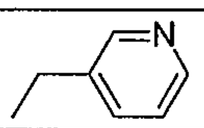
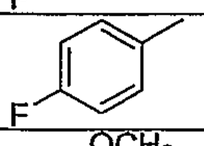
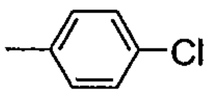
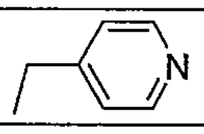
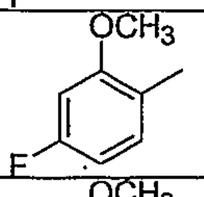
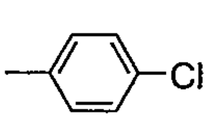
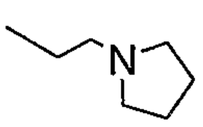
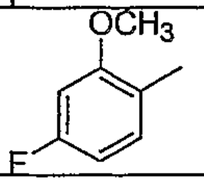
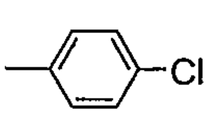
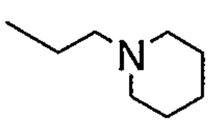
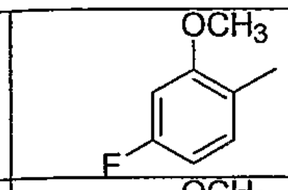
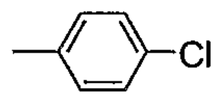
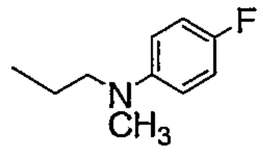
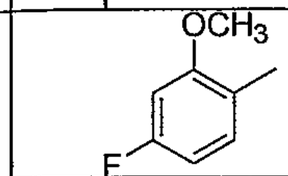
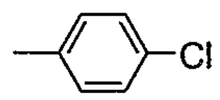
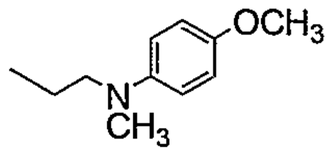
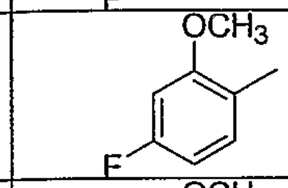
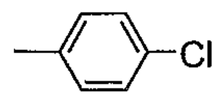
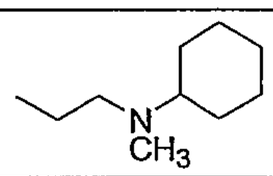
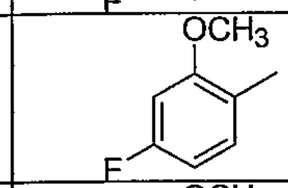
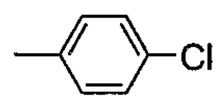
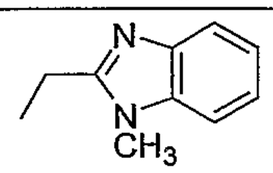
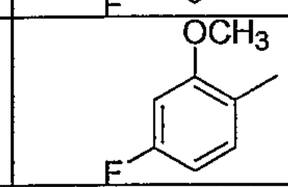
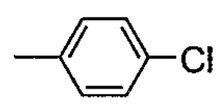
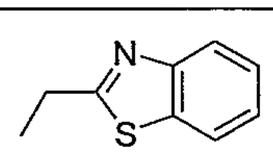
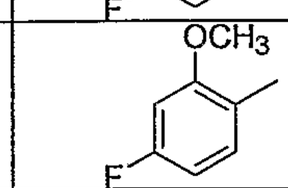
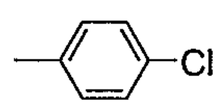
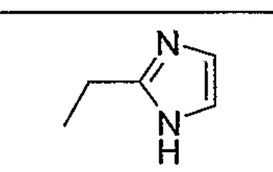
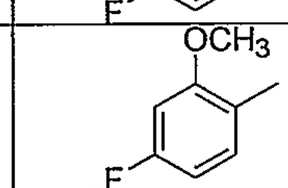
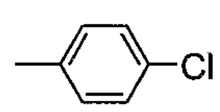
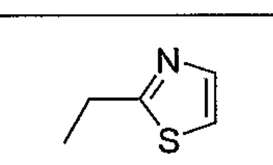
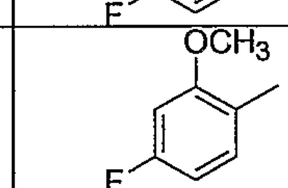
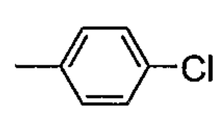
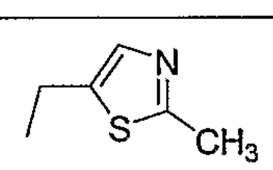
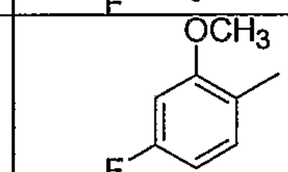
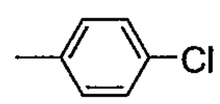
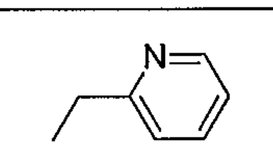
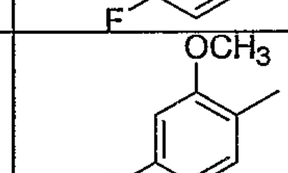
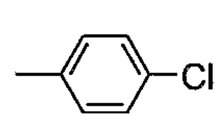
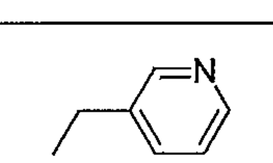
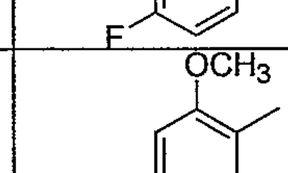
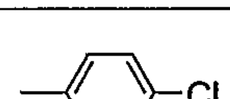
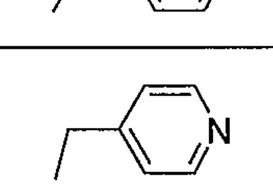
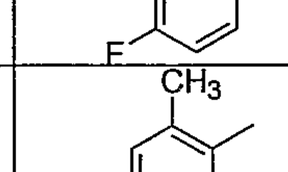
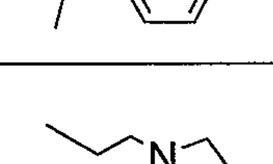
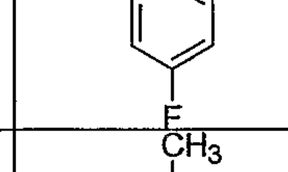
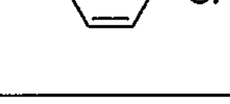
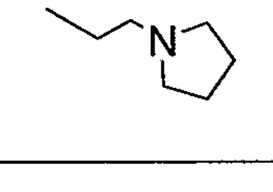
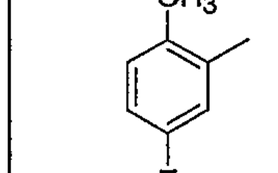
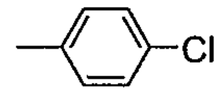
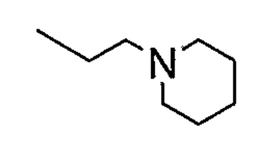
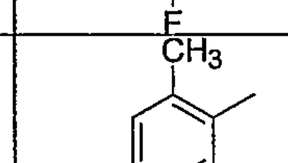
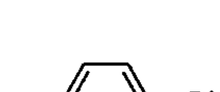
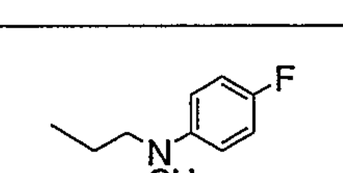
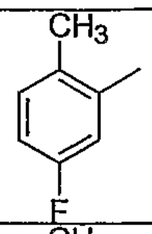
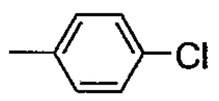
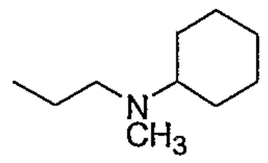
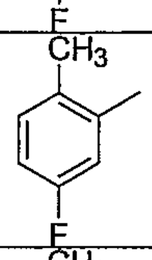
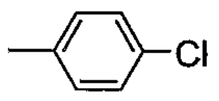
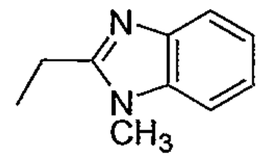
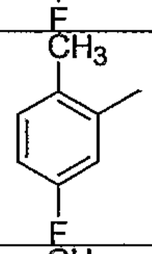
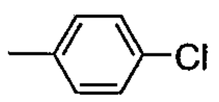
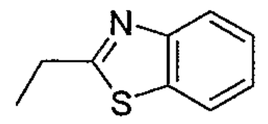
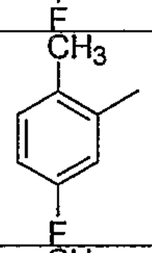
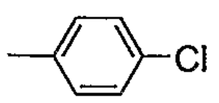
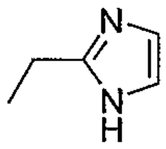
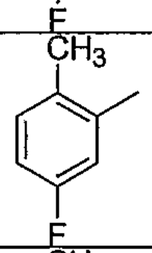
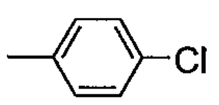
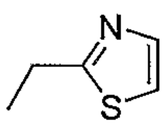
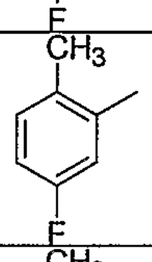
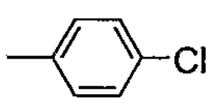
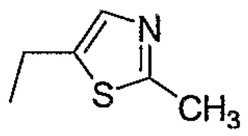
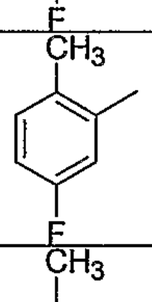
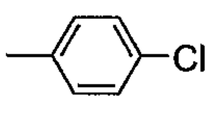
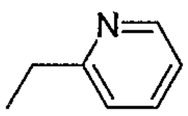
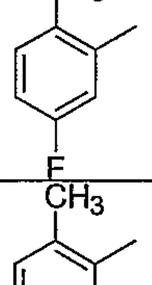
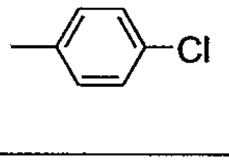
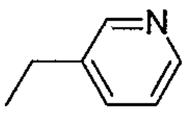
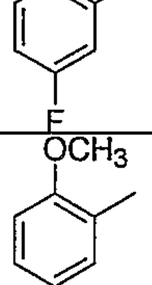
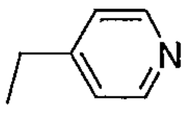
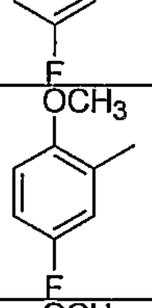
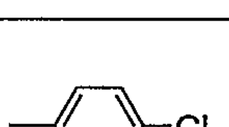
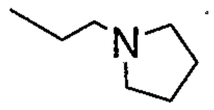
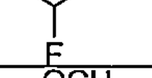
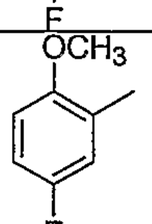
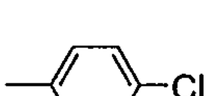
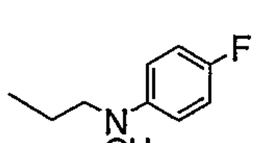
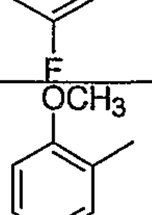
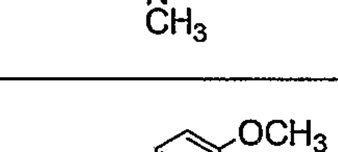
C838			
C839			
C840			
C841			

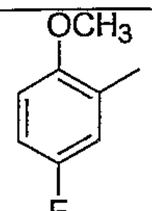
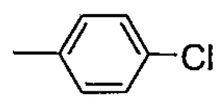
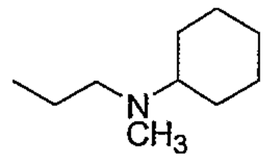
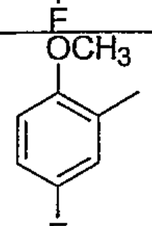
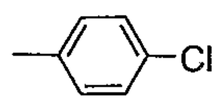
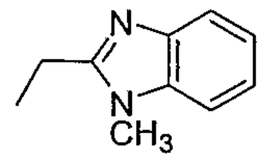
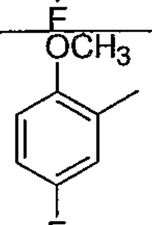
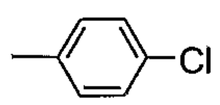
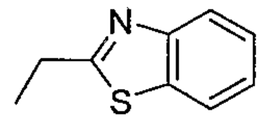
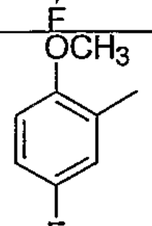
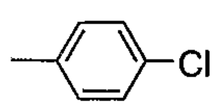
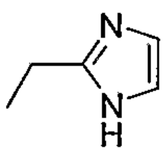
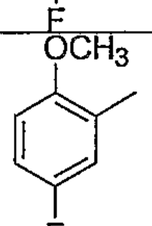
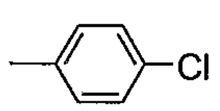
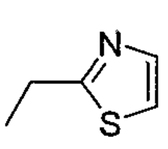
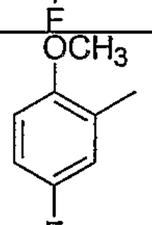
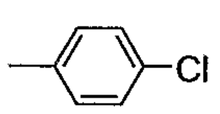
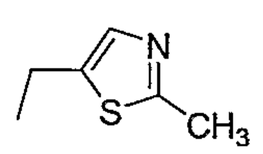
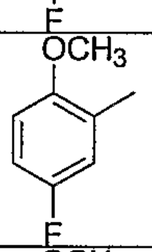
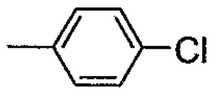
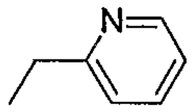
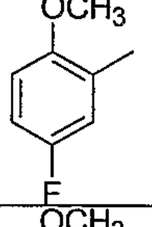
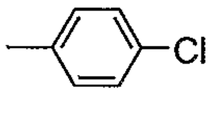
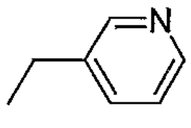
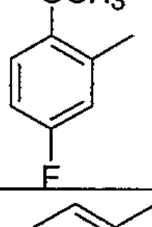
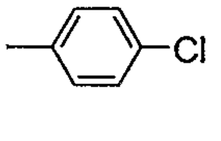
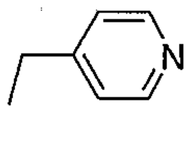
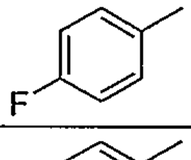
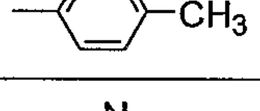
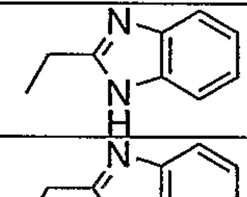
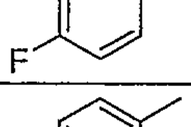
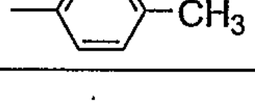
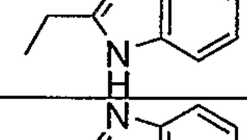
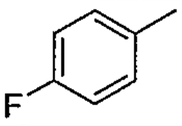
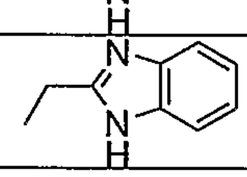
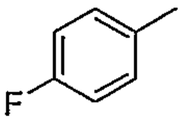
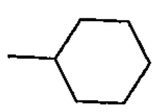
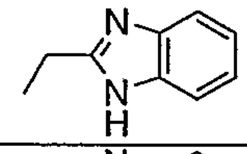
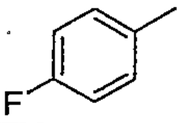
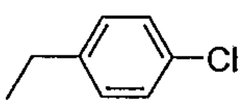
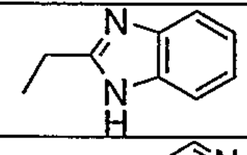
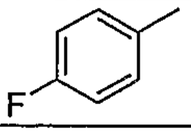
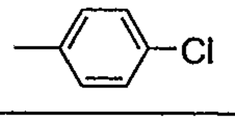
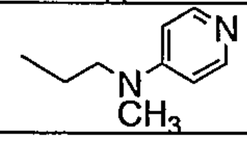
C842			
C843			
C844			
C845			
C846			
C847			
C848			
C849			
C850			
C851			
C852			
C853			
C854			
C855			
C856			
C857			

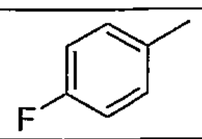
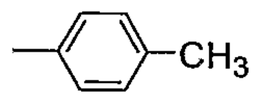
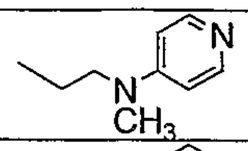
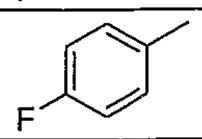
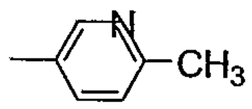
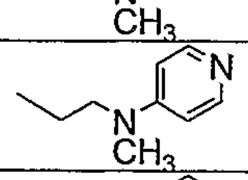
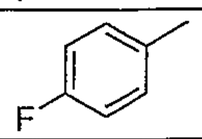
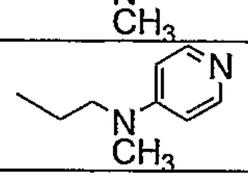
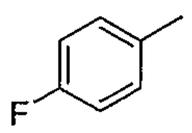
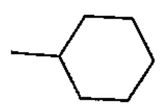
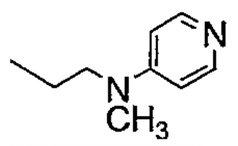
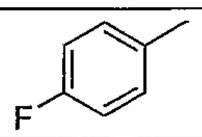
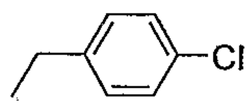
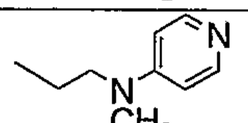
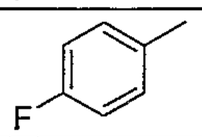
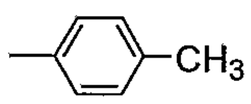
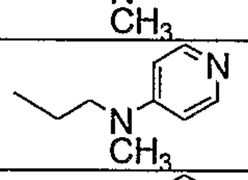
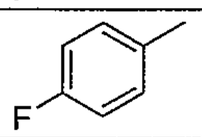
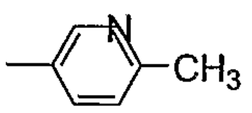
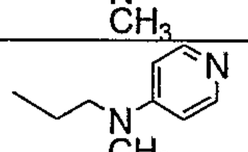
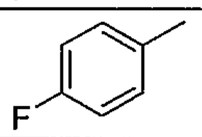
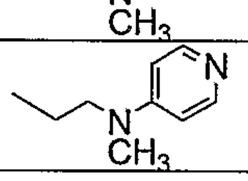
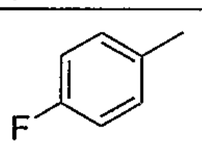
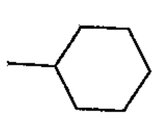
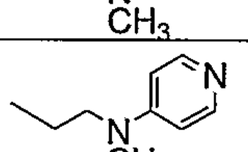
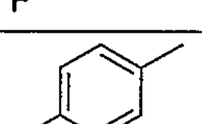
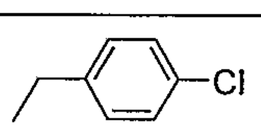
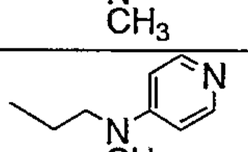
C858			
C859			
C860			
C861			
C862			
C863			
C864			
C865			
C866			
C867			
C868			
C869			
C870			
C871			
C872			
C873			
C874			
C875			
C876			
C877			

C878			
C879			
C880			
C881			
C882			
C883			
C884			
C885			
C886			
C887			
C888			
C889			
C890			
C891			
C892			
C893			
C894			
C895			
C896			
C897			

C898			
C899			
C900			
C901			
C902			
C903			
C904			
C905			
C906			
C907			
C908			
C909			
C910			
C911			
C912			

C913			
C914			
C915			
C916			
C917			
C918			
C919			
C920			
C921			
C922			
C923			
C924			
C925			

C926			
C927			
C928			
C929			
C930			
C931			
C932			
C933			
C934			
C935			
C936			
C937		CH_3	
C938			
C939			
C940			

C941			
C942			
C943		CH_3	
C944			
C945			
C946			
C947			
C948		CH_3	
C949			
C950			

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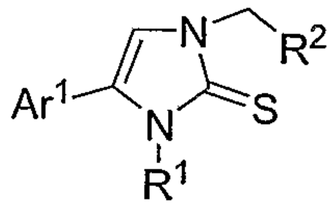

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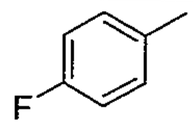
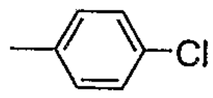
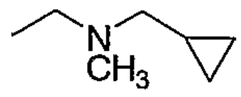
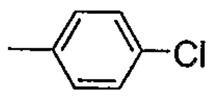
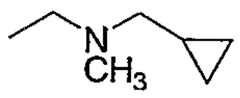
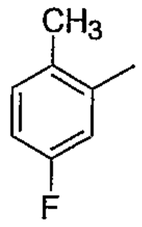
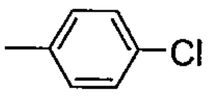
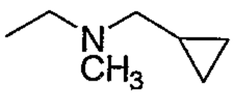
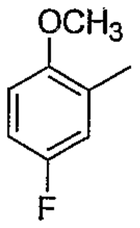
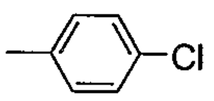
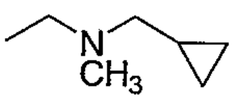
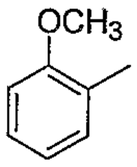
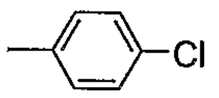
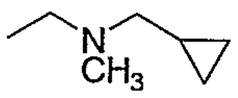
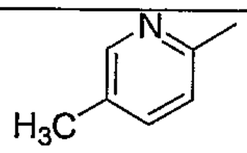
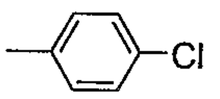
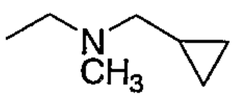
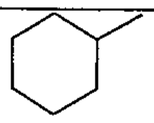
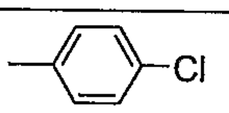
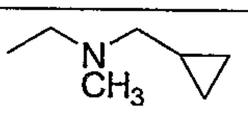
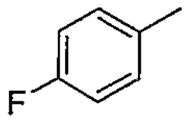
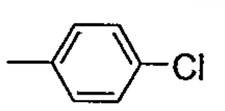
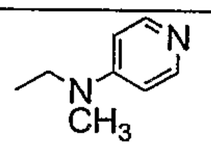
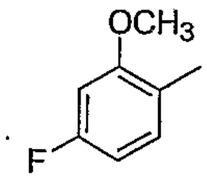
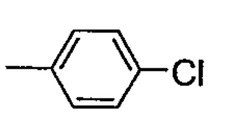
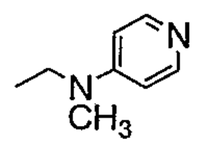
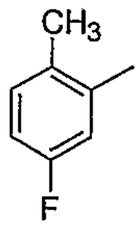
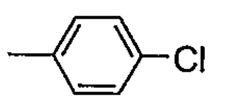
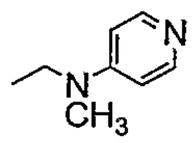
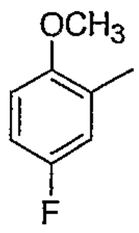
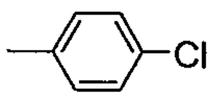
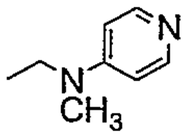
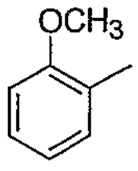
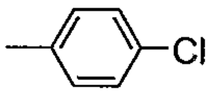
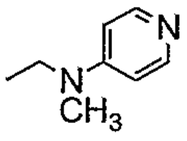
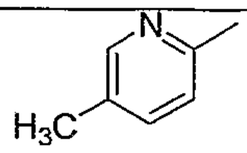
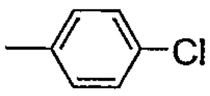
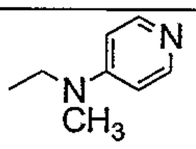
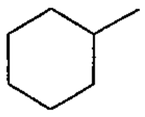
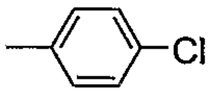
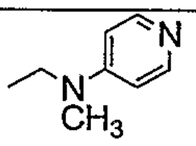
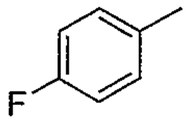
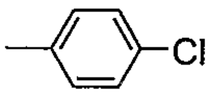
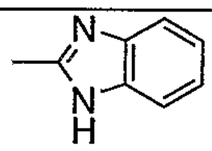
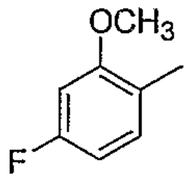
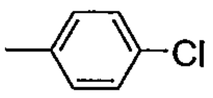
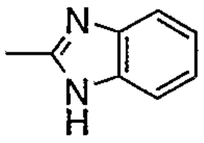
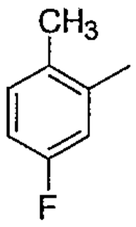
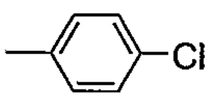
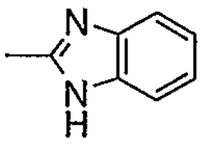
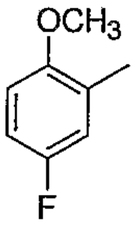
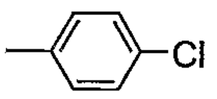
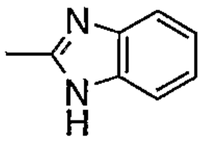
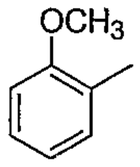
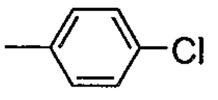
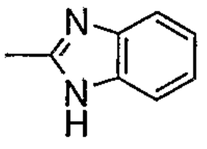
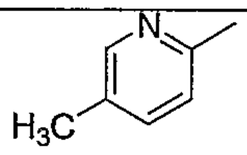
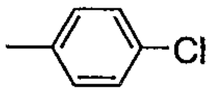
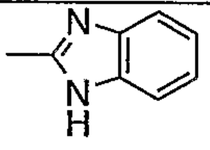
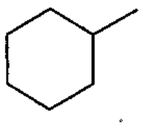
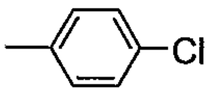
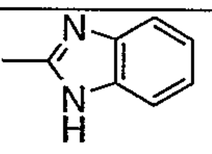
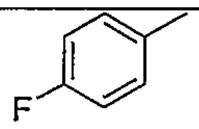
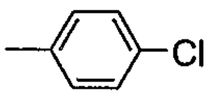
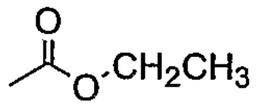
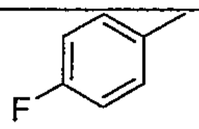
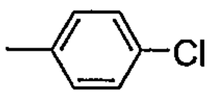
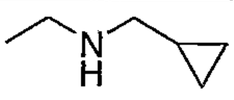
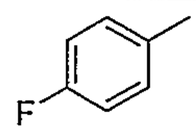
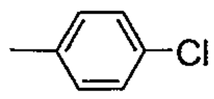
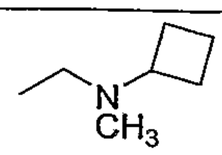
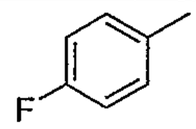
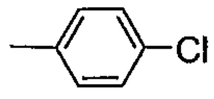
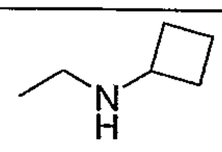
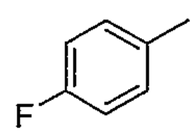
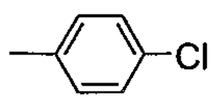
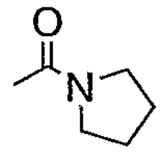
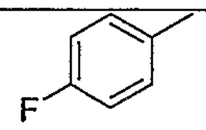
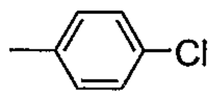
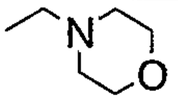
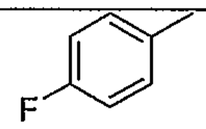
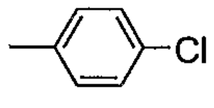
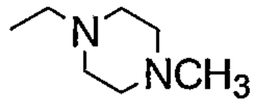
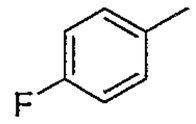
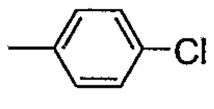
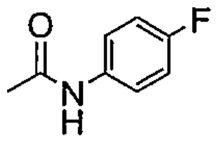
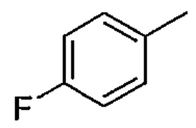
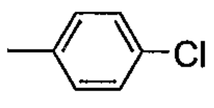
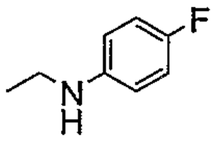
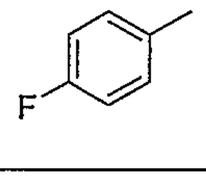
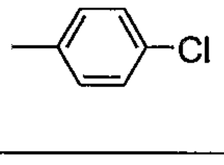
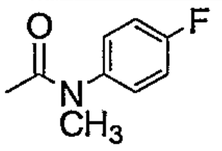
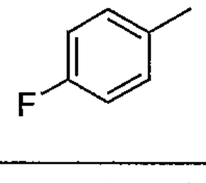
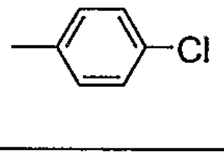
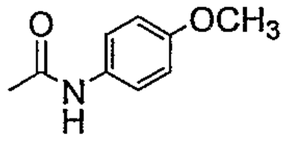
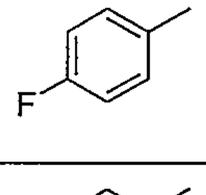
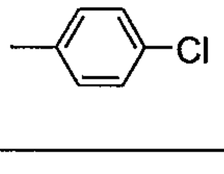
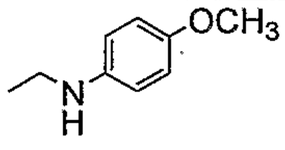
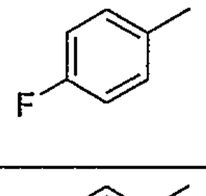
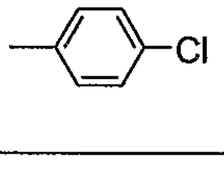
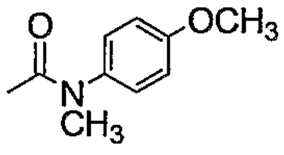
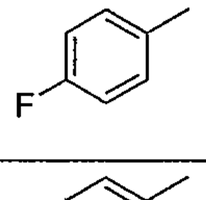
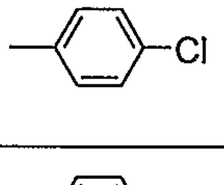
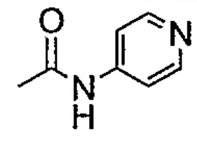
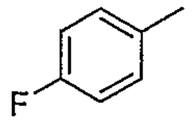
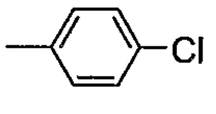
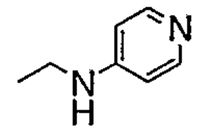
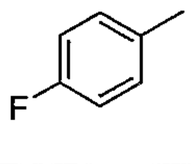
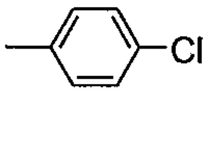
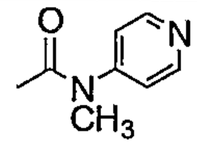
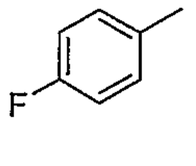
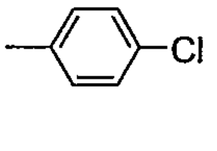
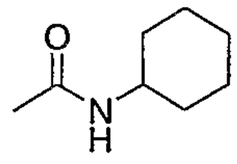
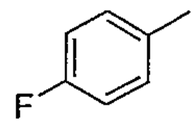
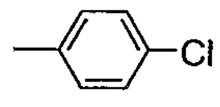
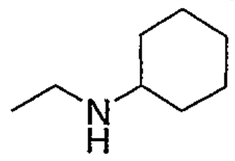
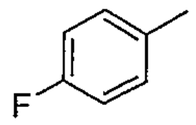
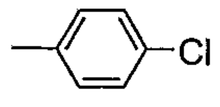
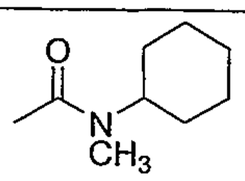
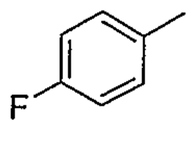
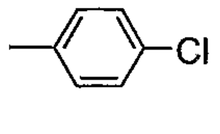
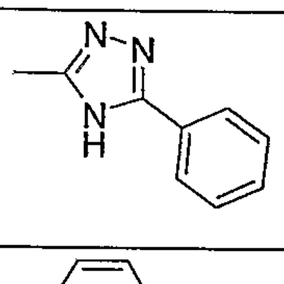
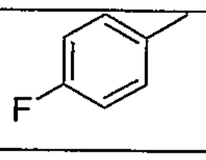
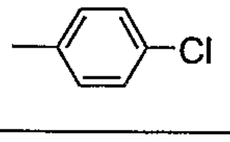
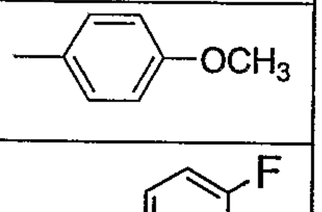
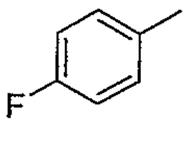
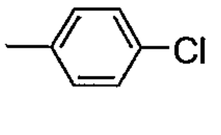
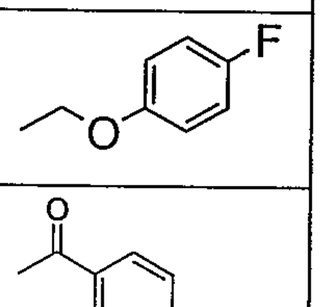
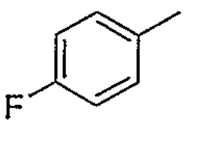
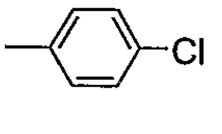
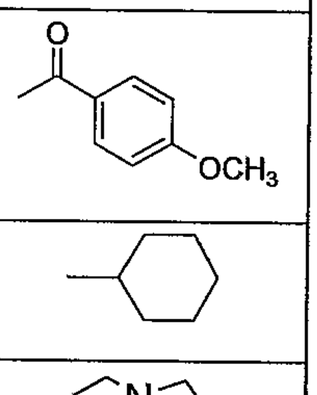
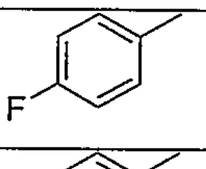
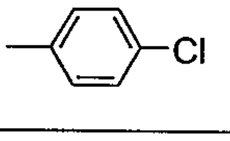
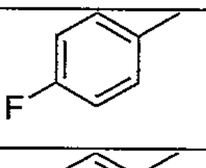
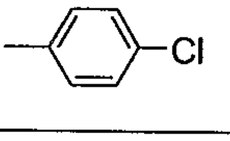
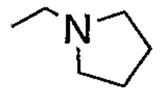
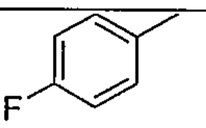
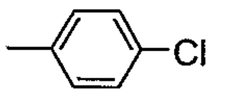
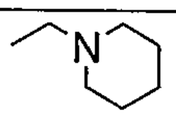
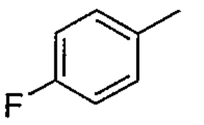
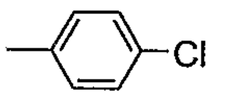
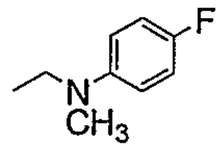
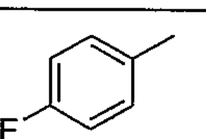
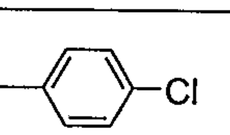
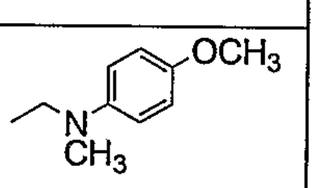
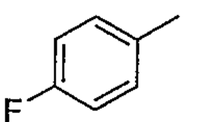
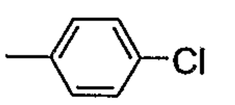
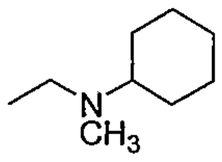
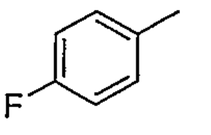
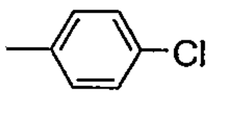
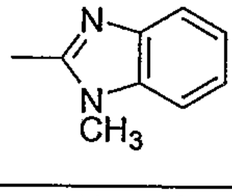
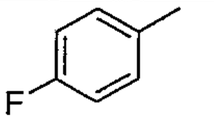
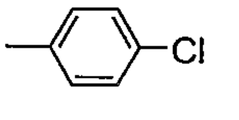
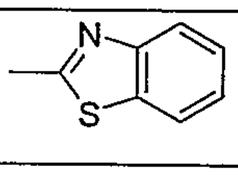
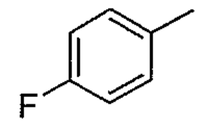
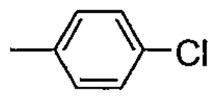
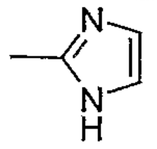
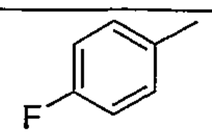
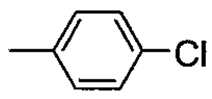
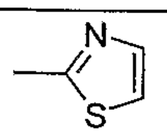
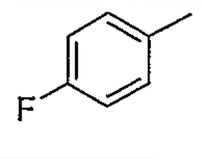
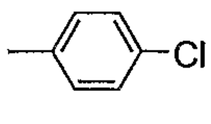
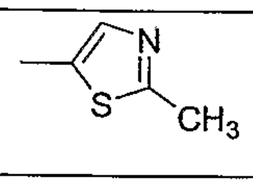
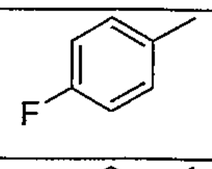
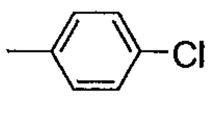
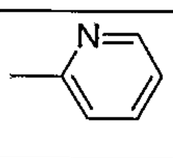
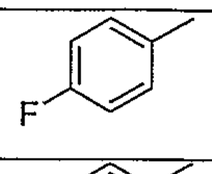
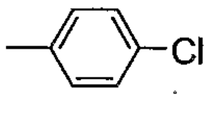
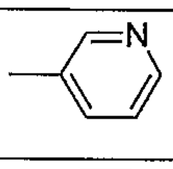
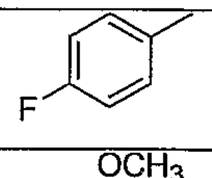
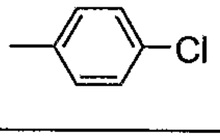
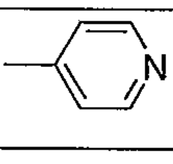
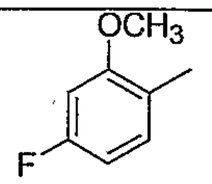
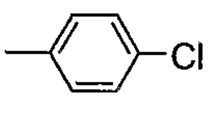
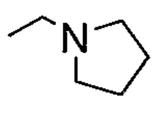
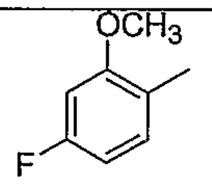
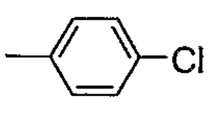
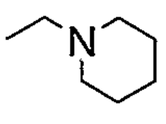
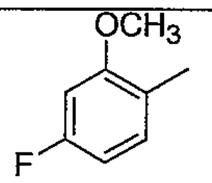
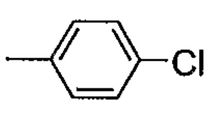
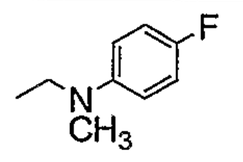
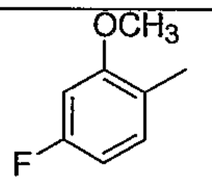
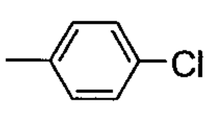
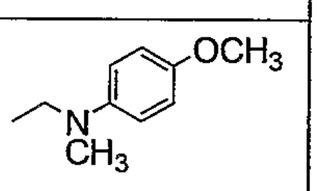
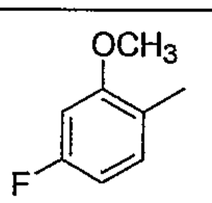
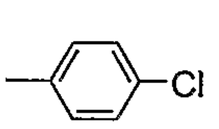
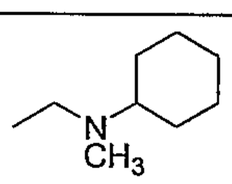
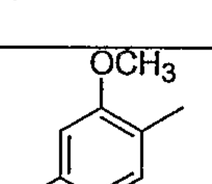
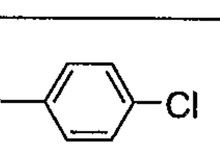
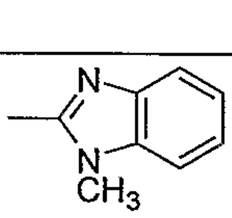
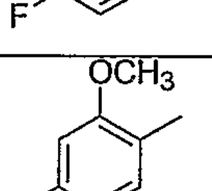
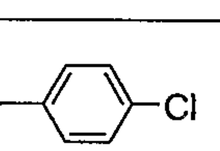
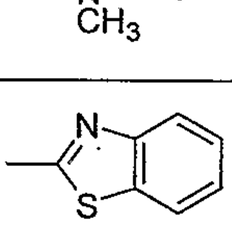
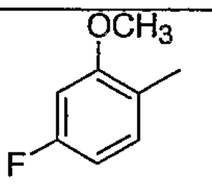
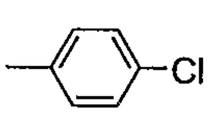
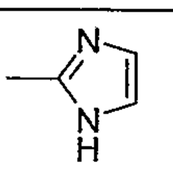
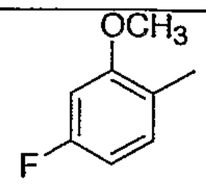
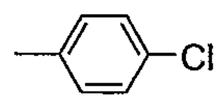
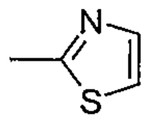
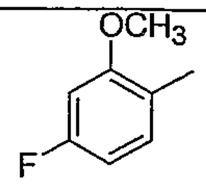
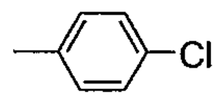
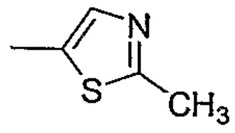
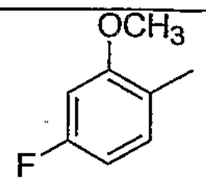
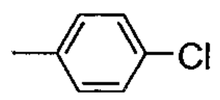
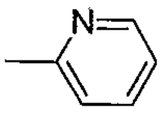
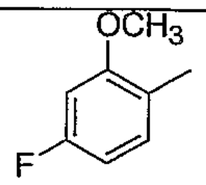
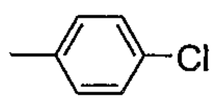
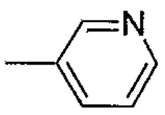
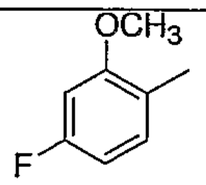
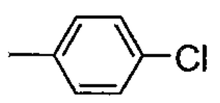
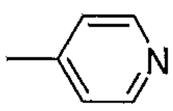
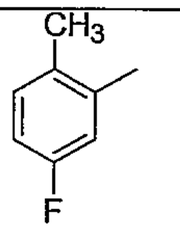
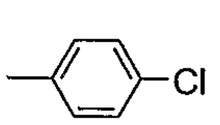
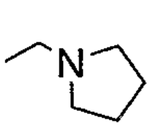
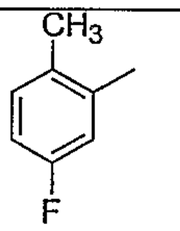
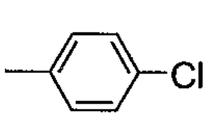
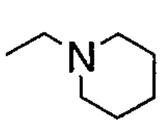
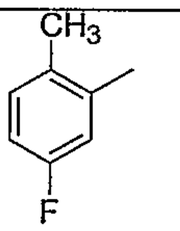
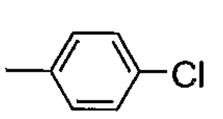
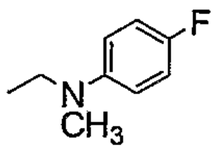
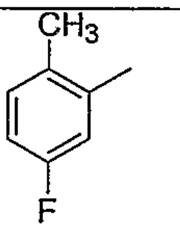
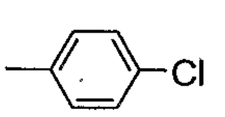
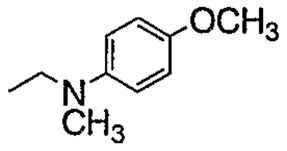
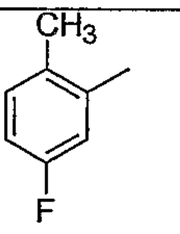
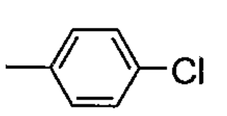
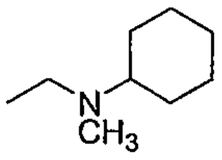
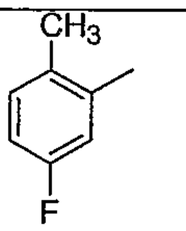
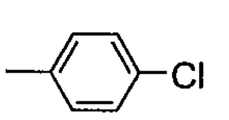
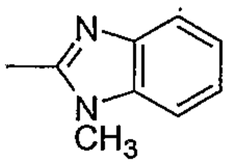
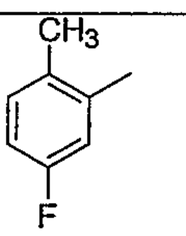
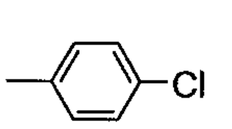
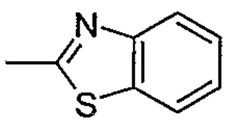
D1			
D2			
D3			
D4			
D5			
D6			
D7			
D8			
D9			
D10			

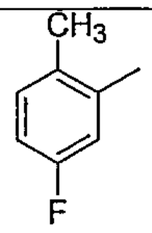
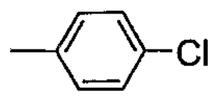
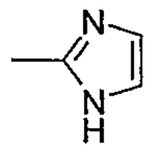
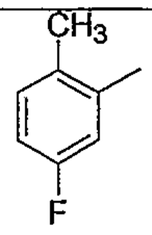
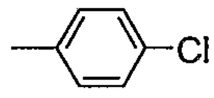
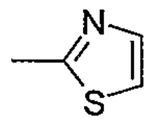
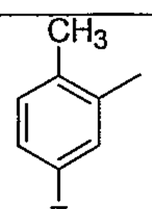
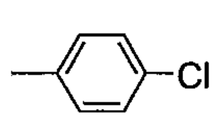
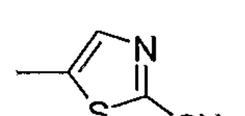
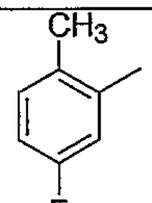
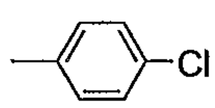
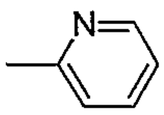
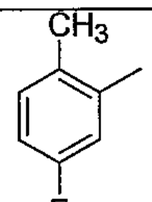
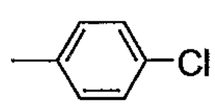
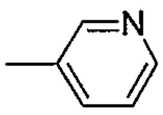
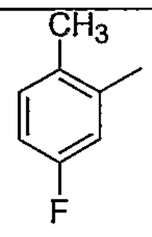
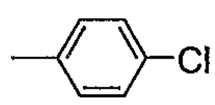
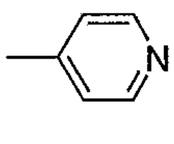
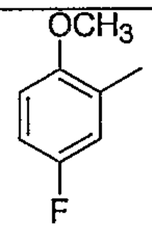
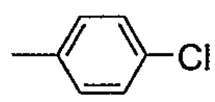
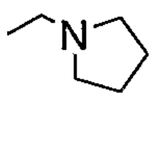
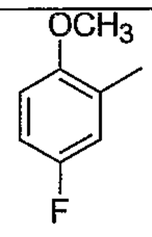
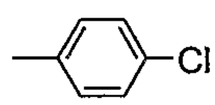
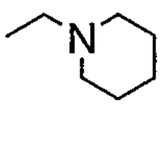
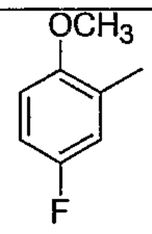
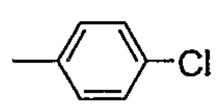
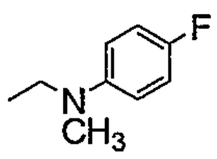
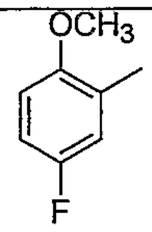
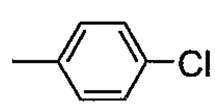
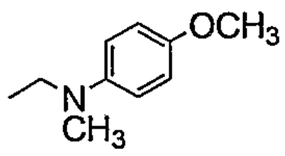
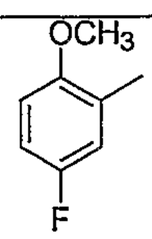
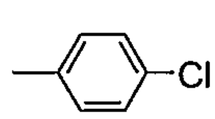
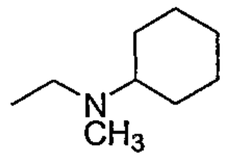
D11			
D12			
D13			
D14			
D15			
D16			
D17			
D18			
D19			
D20			
D21			
D22			
D23			

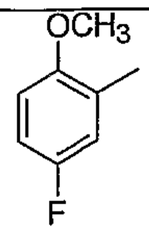
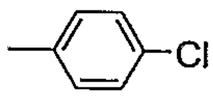
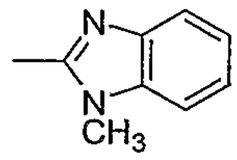
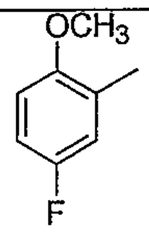
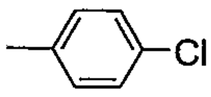
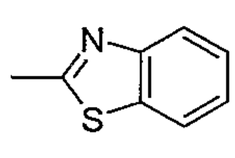
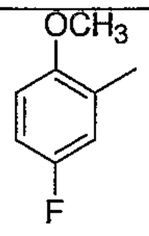
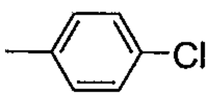
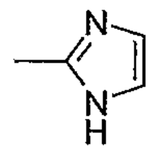
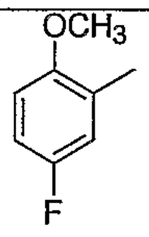
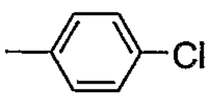
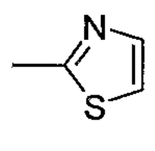
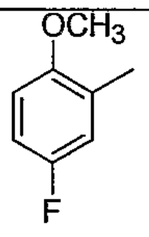
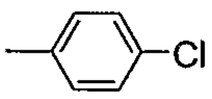
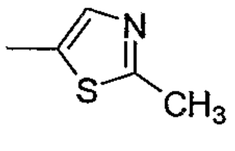
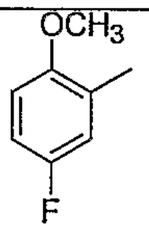
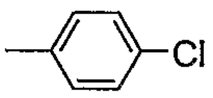
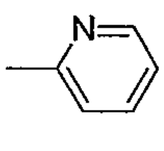
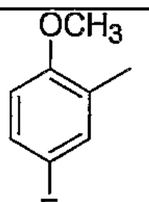
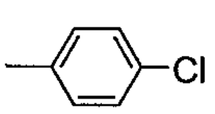
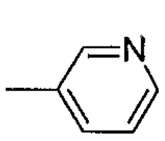
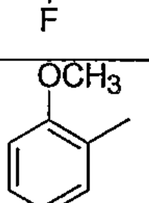
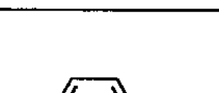
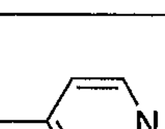
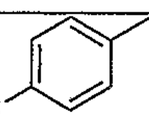
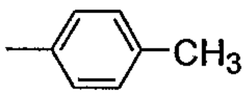
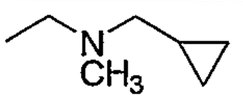
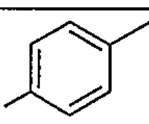
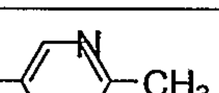
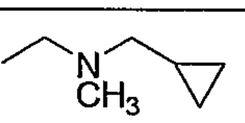
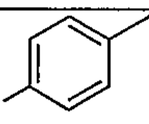
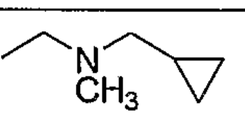
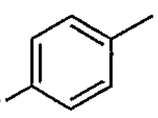
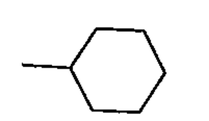
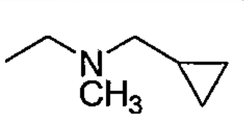
D24			
D25			
D26			
D27			
D28			
D29			
D30			
D31			
D32			
D33			
D34			
D35			
D36			
D37			
D38			

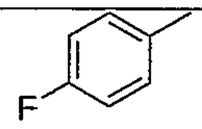
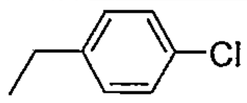
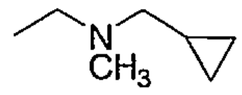
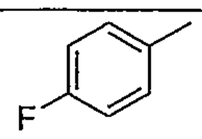
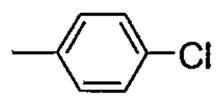
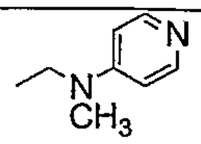
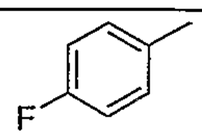
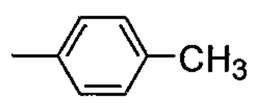
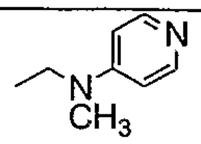
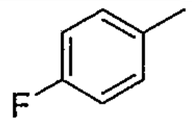
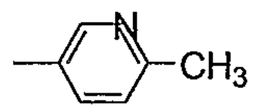
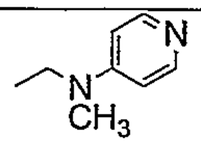
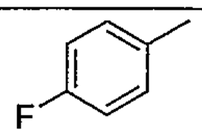
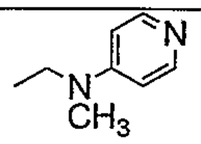
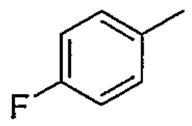
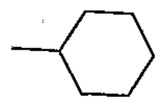
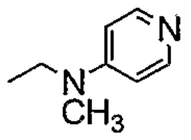
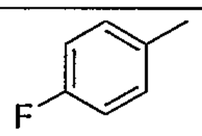
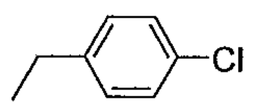
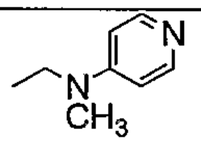
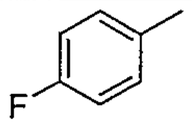
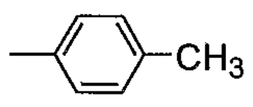
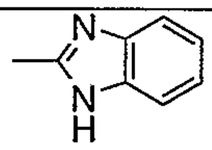
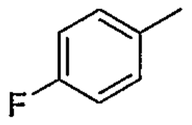
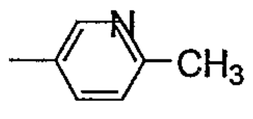
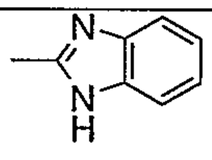
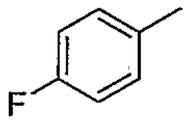
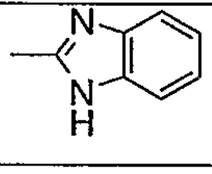
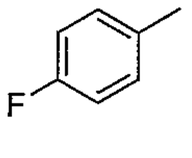
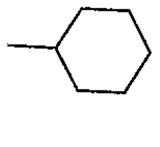
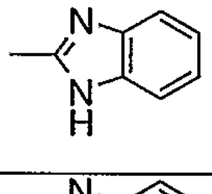
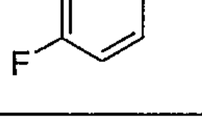
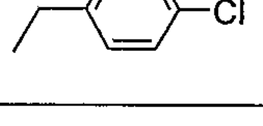
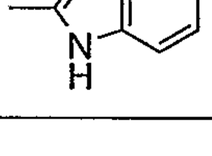
D39			
D40			
D41			
D42			
D43			
D44			
D45			
D46			
D47			
D48			
D49			
D50			
D51			
D52			

D53			
D54			
D55			
D56			
D57			
D58			
D59			
D60			
D61			
D62			
D63			
D64			
D65			
D66			

D67			
D68			
D69			
D70			
D71			
D72			
D73			
D74			
D75			
D76			
D77			
D78			

D79			
D80			
D81			
D82			
D83			
D84			
D85			
D86			
D87			
D88			
D89			

D90			
D91			
D92			
D93			
D94			
D95			
D96			
D97			
D98			
D99			
D100		CH_3	
D101			

D102			
D103			
D104			
D105			
D106		CH_3	
D107			
D108			
D109			
D110			
D111		CH_3	
D112			
D113			

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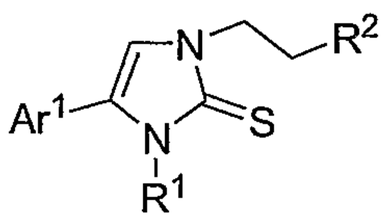

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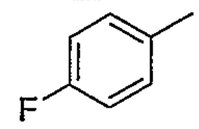
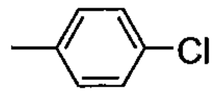
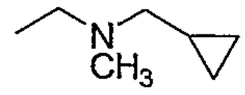
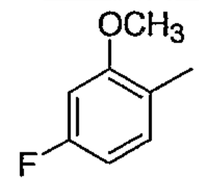
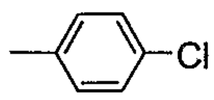
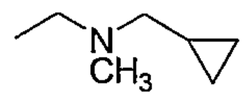
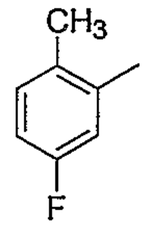
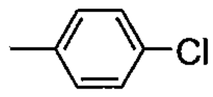
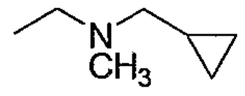
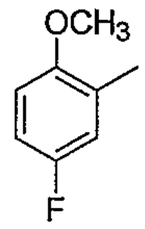
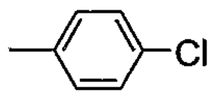
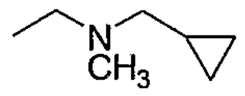
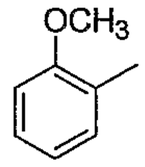
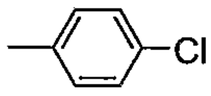
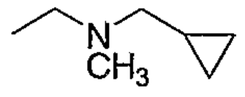
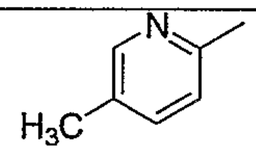
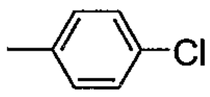
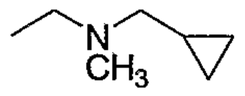
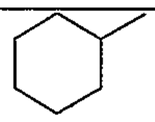
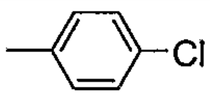
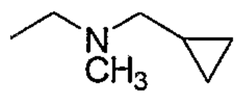
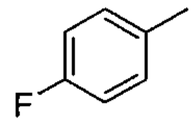
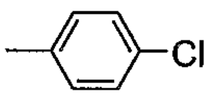
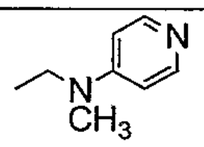
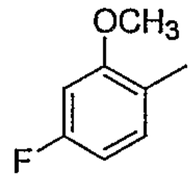
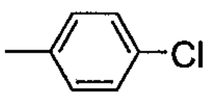
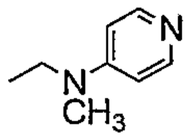
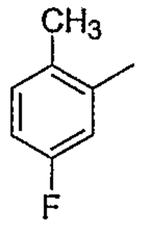
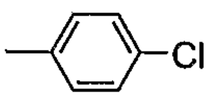
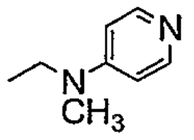
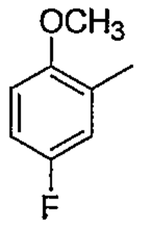
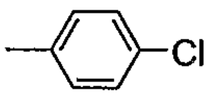
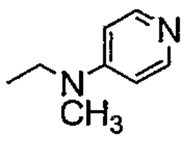
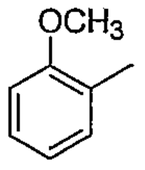
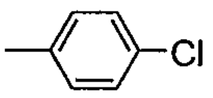
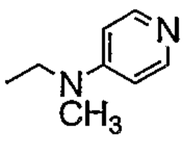
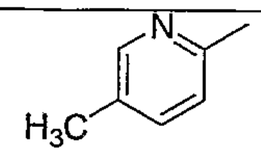
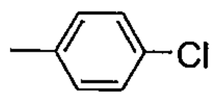
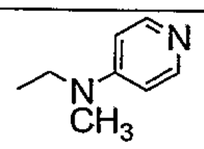
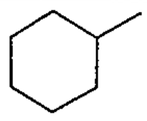
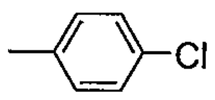
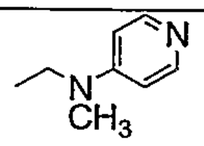
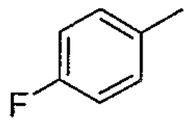
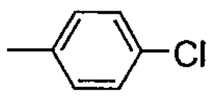
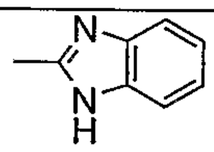
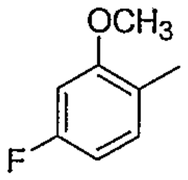
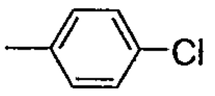
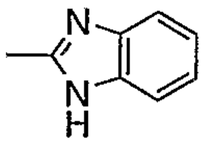
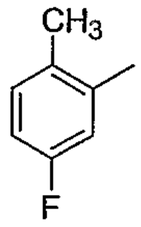
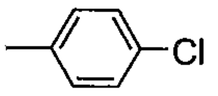
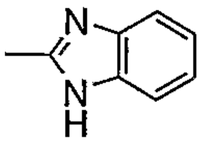
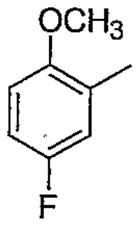
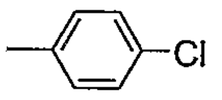
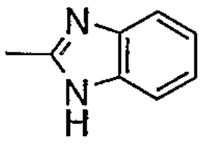
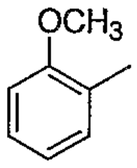
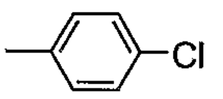
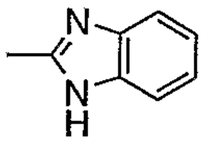
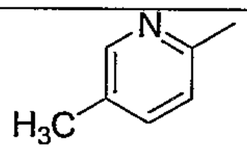
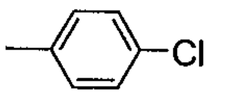
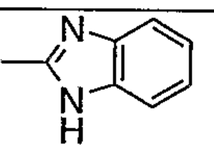
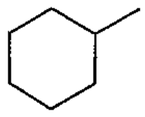
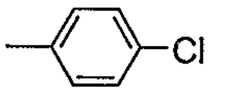
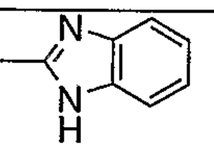
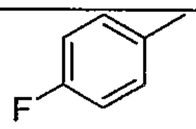
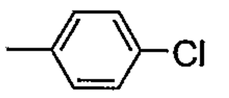
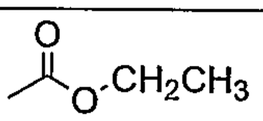
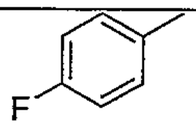
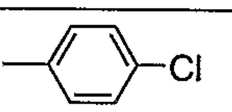
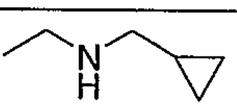
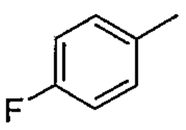
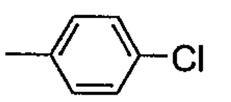
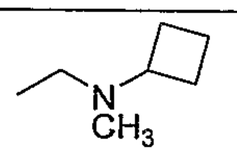
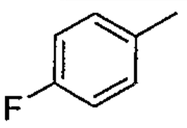
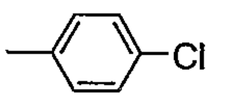
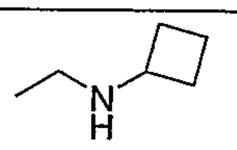
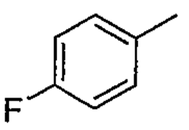
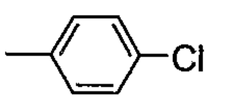
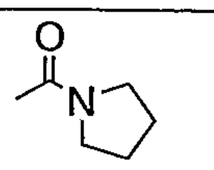
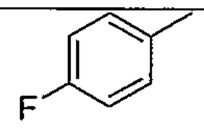
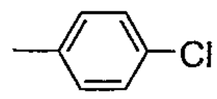
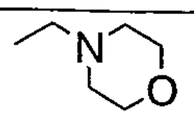
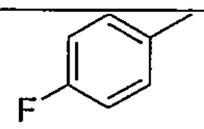
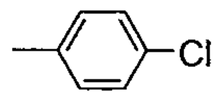
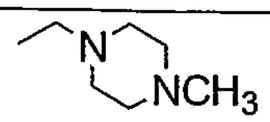
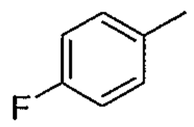
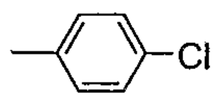
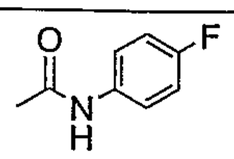
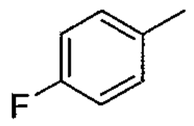
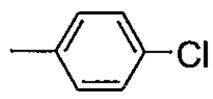
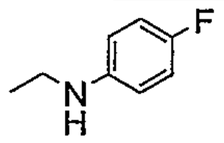
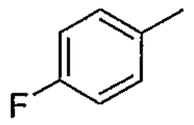
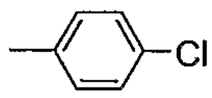
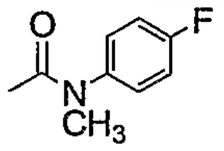
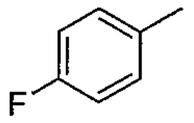
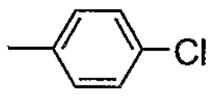
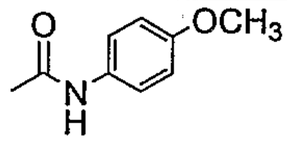
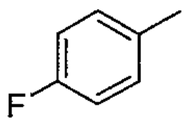
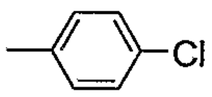
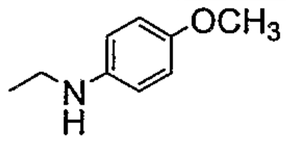
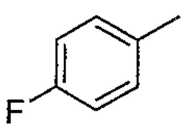
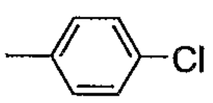
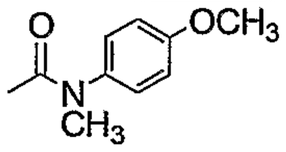
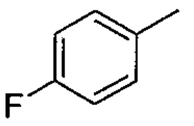
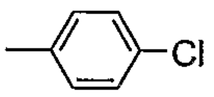
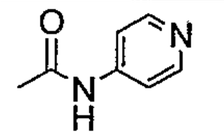
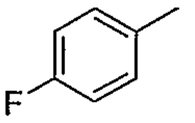
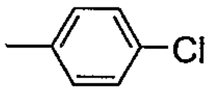
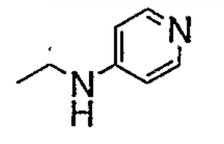
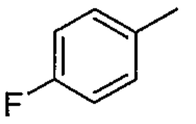
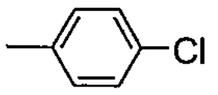
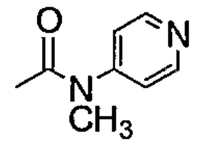
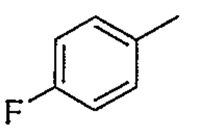
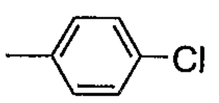
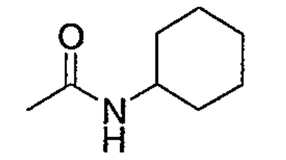
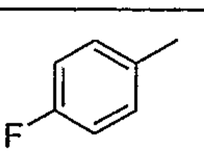
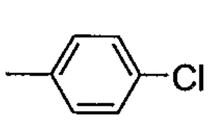
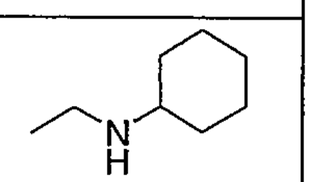
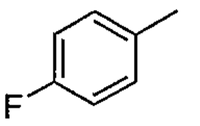
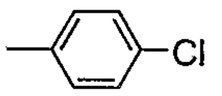
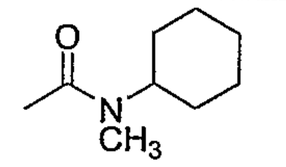
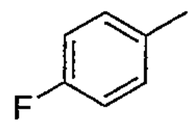
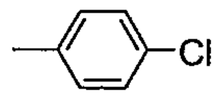
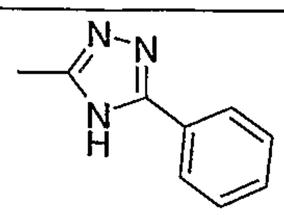
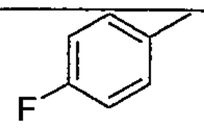
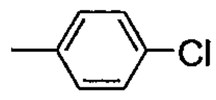
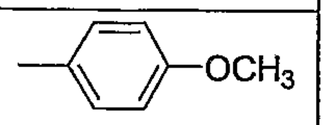
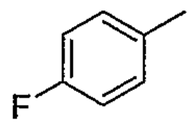
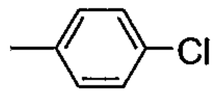
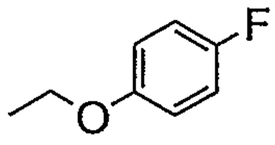
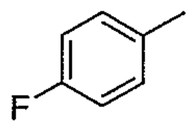
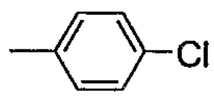
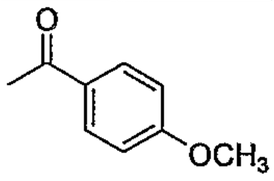
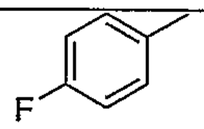
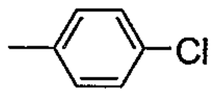
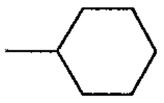
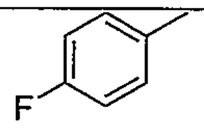
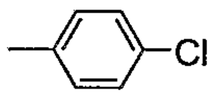
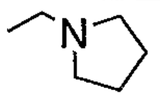
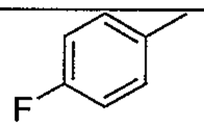
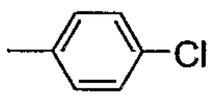
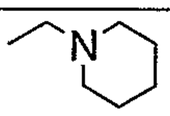
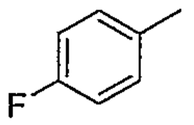
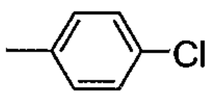
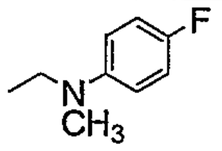
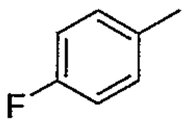
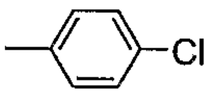
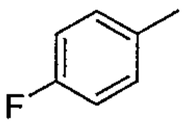
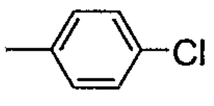
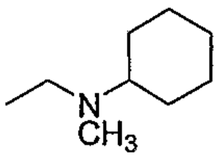
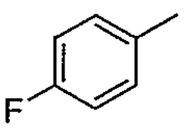
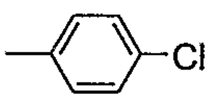
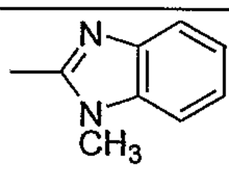
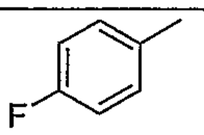
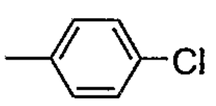
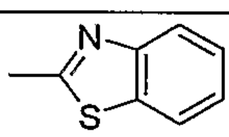
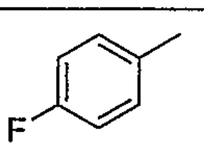
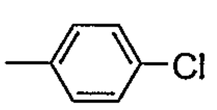
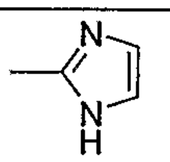
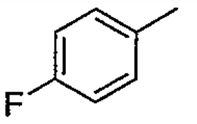
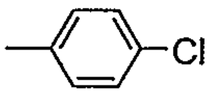
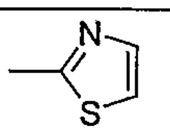
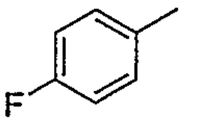
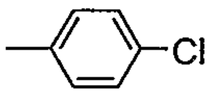
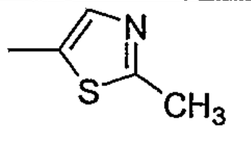
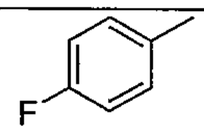
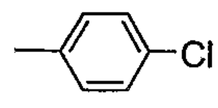
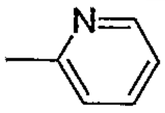
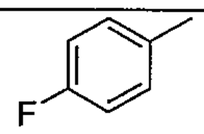
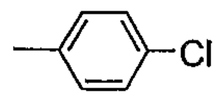
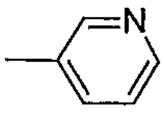
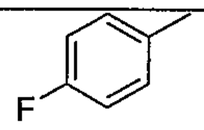
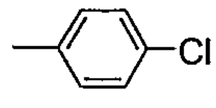
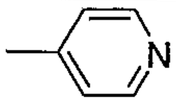
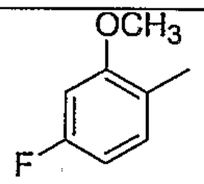
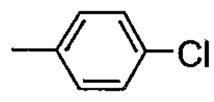
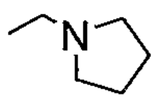
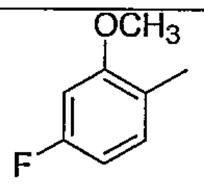
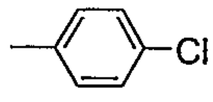
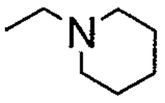
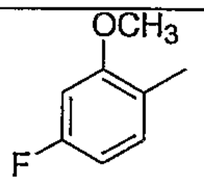
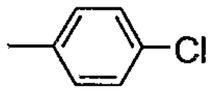
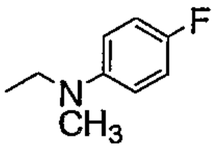
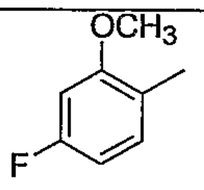
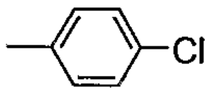
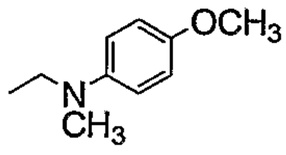
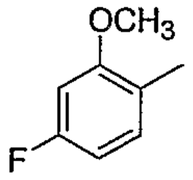
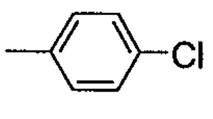
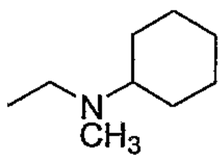
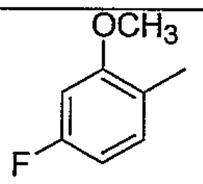
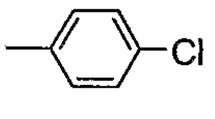
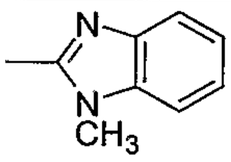
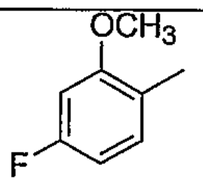
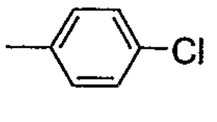
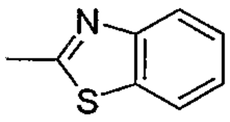
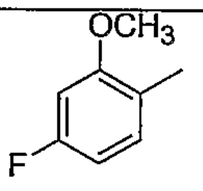
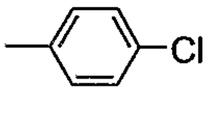
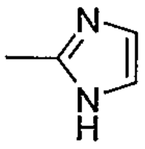
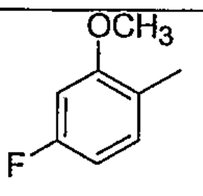
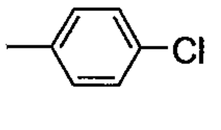
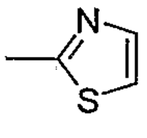
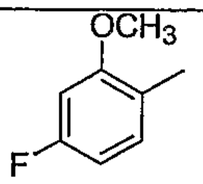
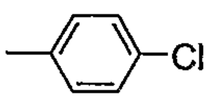
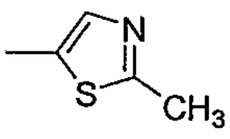
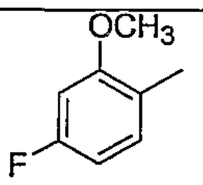
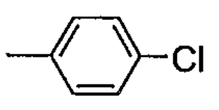
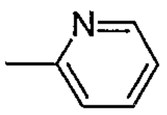
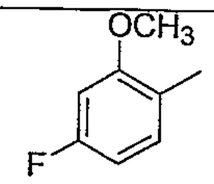
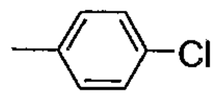
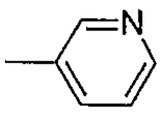
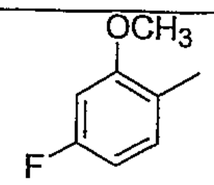
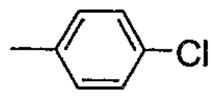
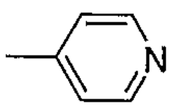
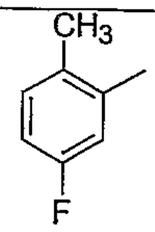
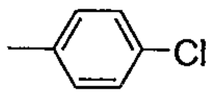
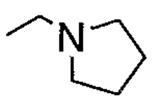
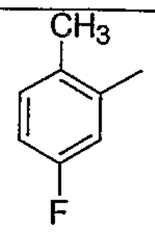
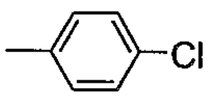
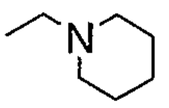
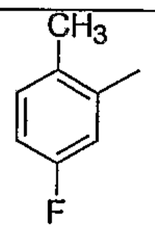
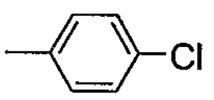
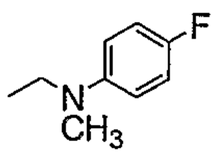
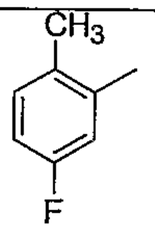
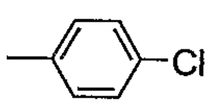
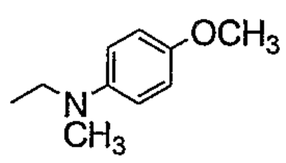
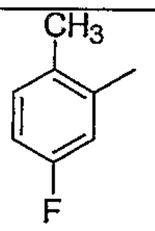
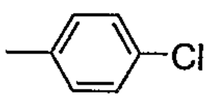
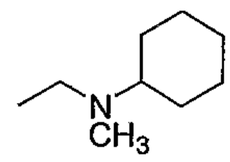
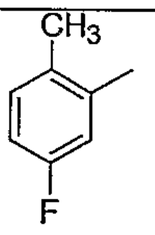
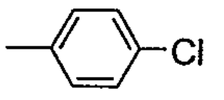
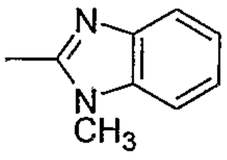
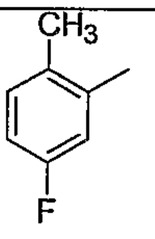
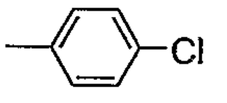
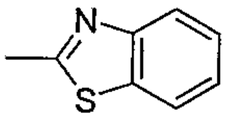
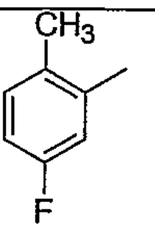
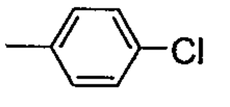
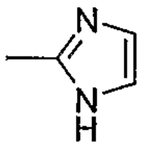
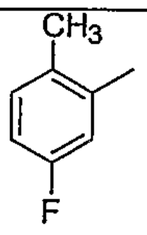
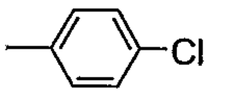
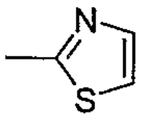
D114			
D115			
D116			
D117			
D118			
D119			
D120			
D121			
D122			
D123			
D124			
D125			

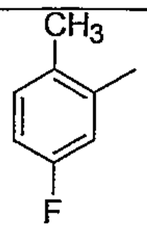
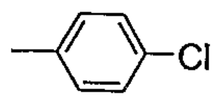
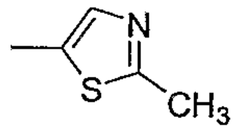
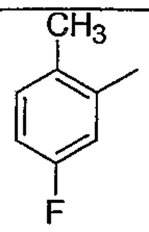
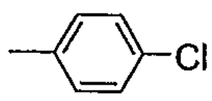
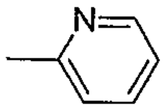
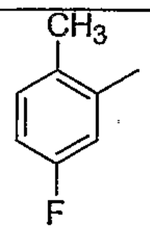
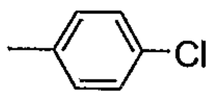
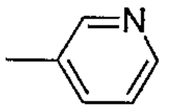
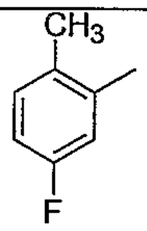
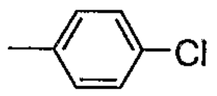
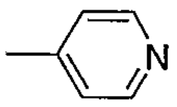
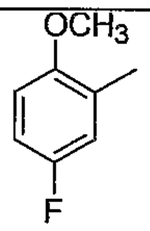
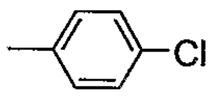
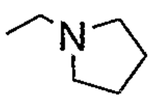
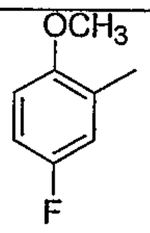
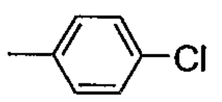
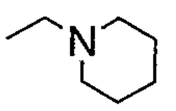
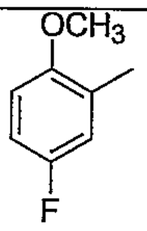
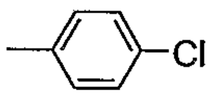
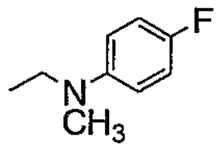
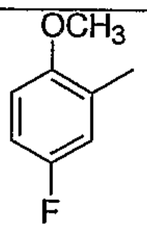
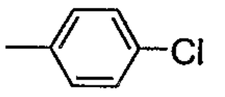
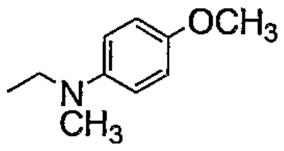
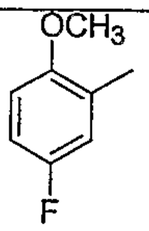
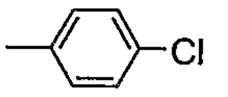
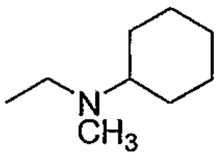
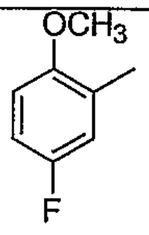
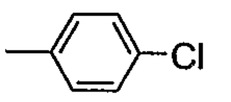
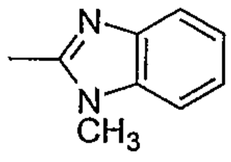
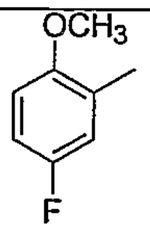
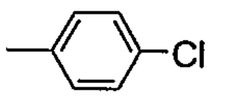
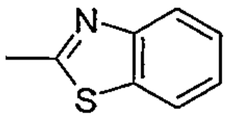
D126			
D127			
D128			
D129			
D130			
D131			
D132			
D133			
D134			
D135			
D136			
D137			
D138			
D139			

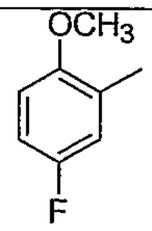
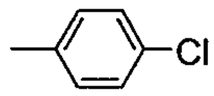
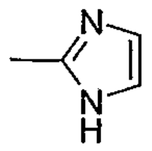
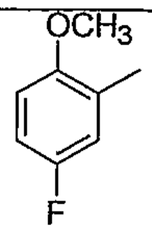
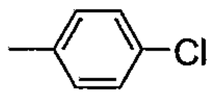
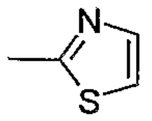
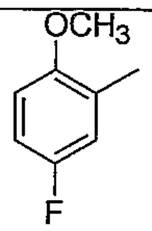
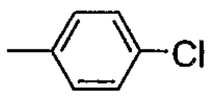
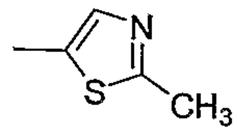
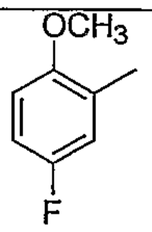
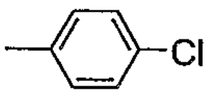
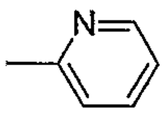
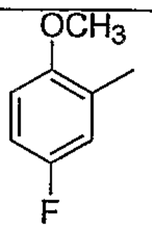
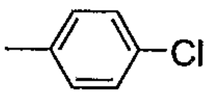
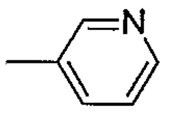
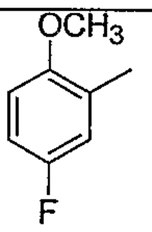
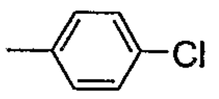
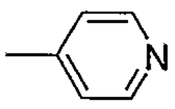
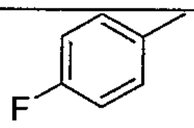
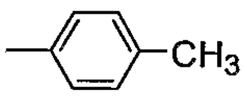
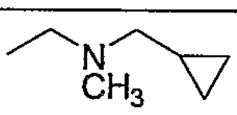
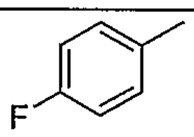
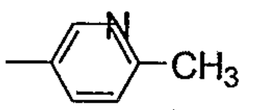
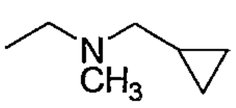
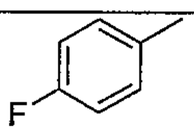
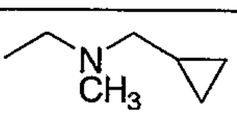
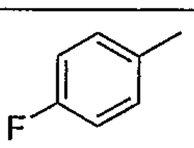
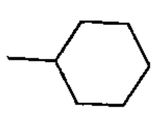
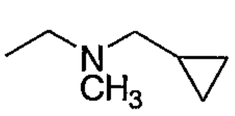
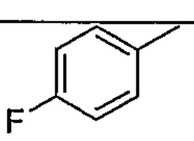
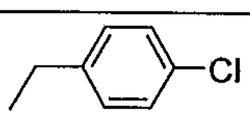
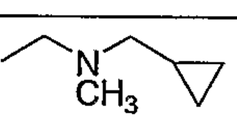
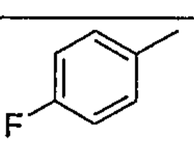
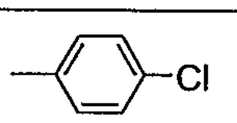
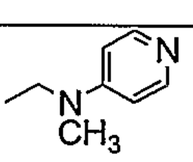
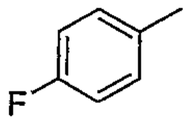
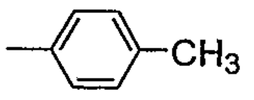
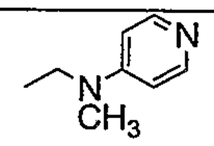
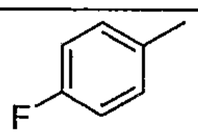
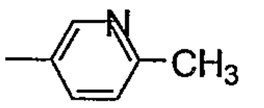
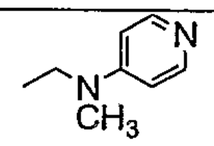
D140			
D141			
D142			
D143			
D144			
D145			
D146			
D147			
D148			
D149			
D150			
D151			
D152			
D153			

D154			
D155			
D156			
D157			
D158			
D159			
D160			
D161			
D162			
D163			
D164			
D165			
D166			
D167			
D168			

D169			
D170			
D171			
D172			
D173			
D174			
D175			
D176			
D177			
D178			
D179			
D180			
D181			
D182			

D183			
D184			
D185			
D186			
D187			
D188			
D189			
D190			
D191			
D192			
D193			

D194			
D195			
D196			
D197			
D198			
D199			
D200			
D201			
D202			
D203			
D204			

D205			
D206			
D207			
D208			
D209			
D210			
D211			
D212			
D213		CH_3	
D214			
D215			
D216			
D217			
D218			

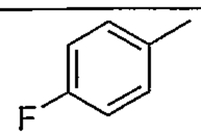
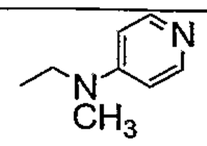
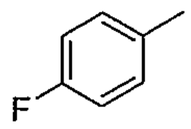
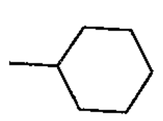
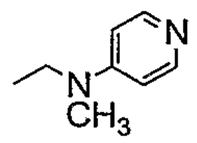
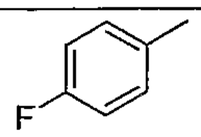
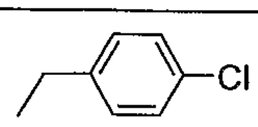
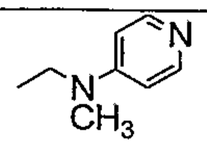
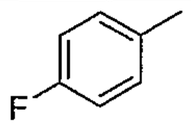
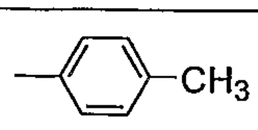
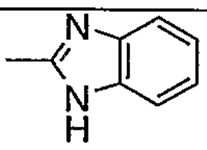
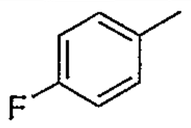
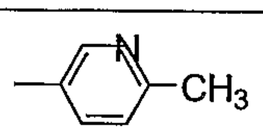
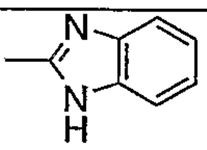
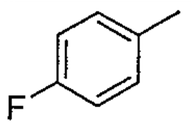
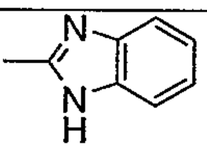
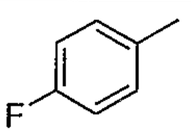
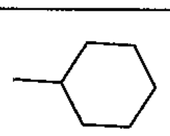
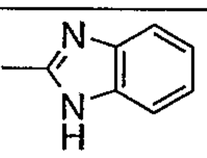
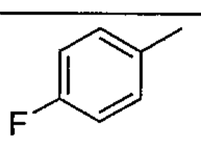
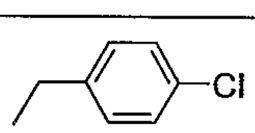
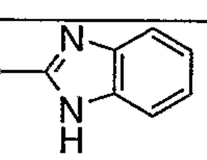
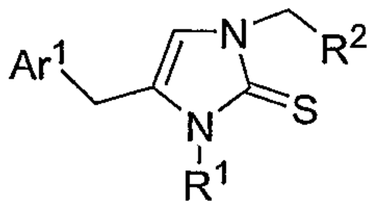
D219		CH_3	
D220			
D221			
D222			
D223			
D224		CH_3	
D225			
D226			

TABLE D-3



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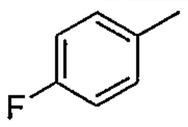
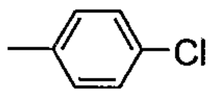
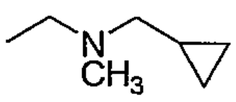
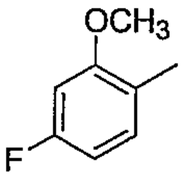
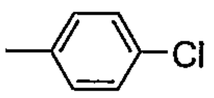
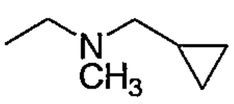
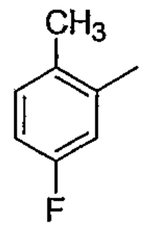
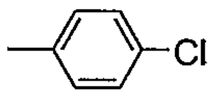
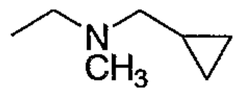
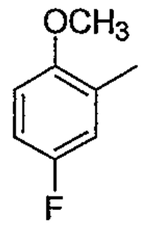
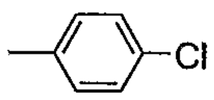
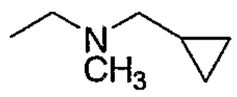
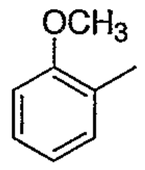
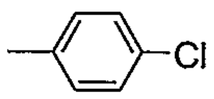
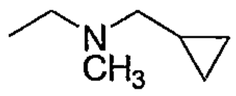
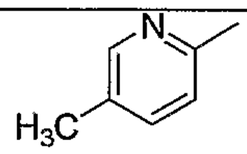
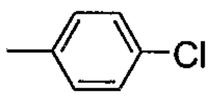
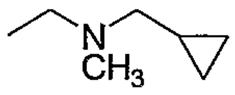
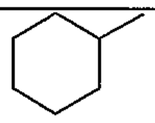
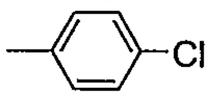
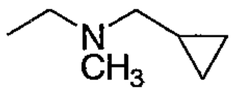
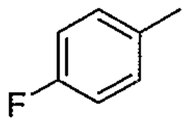
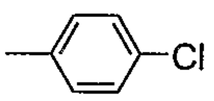
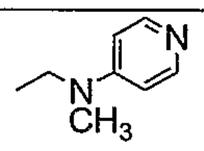
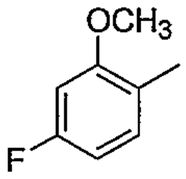
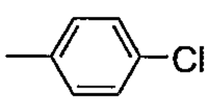
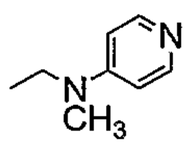
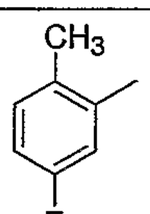
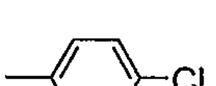
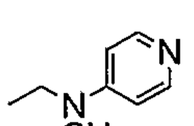
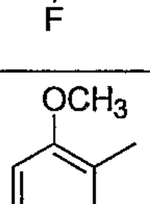
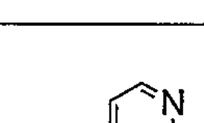
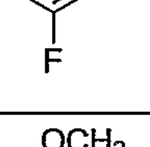
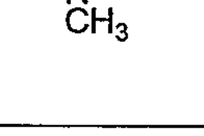
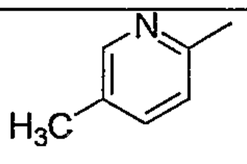
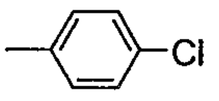
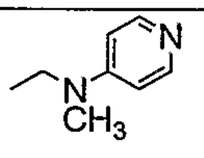
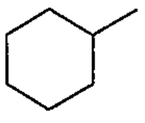
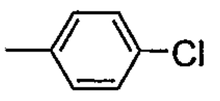
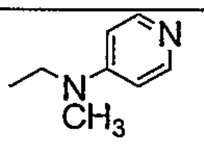
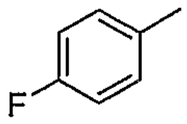
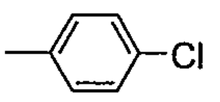
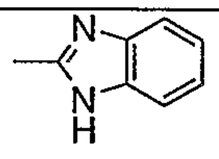
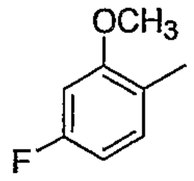
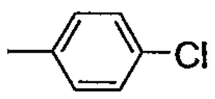
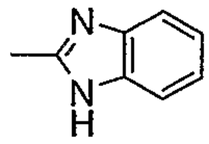
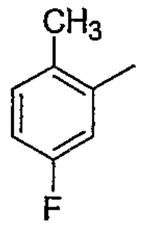
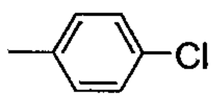
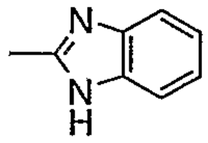
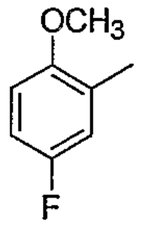
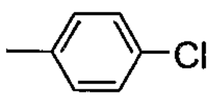
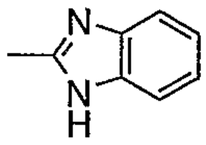
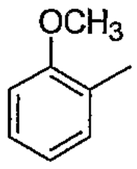
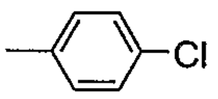
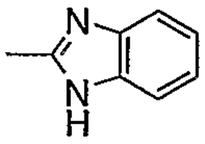
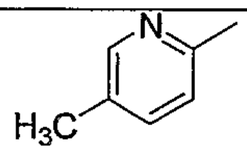
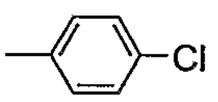
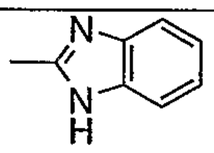
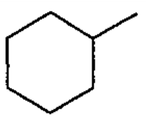
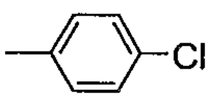
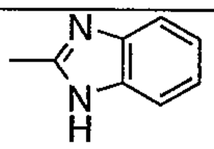
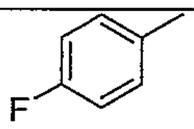
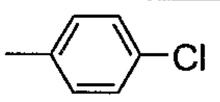
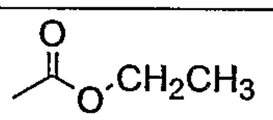
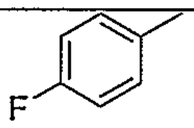
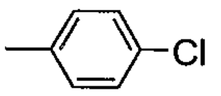
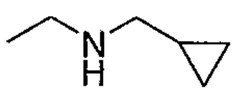
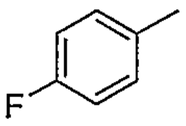
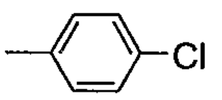
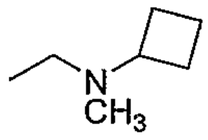
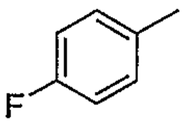
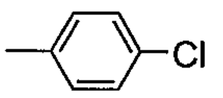
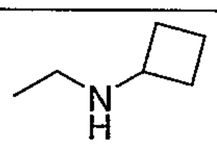
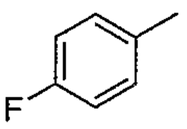
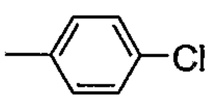
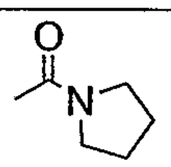
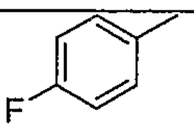
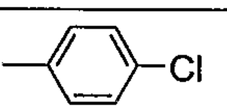
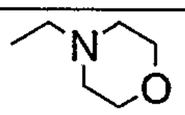
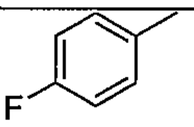
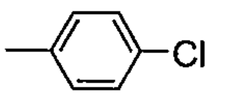
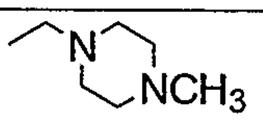
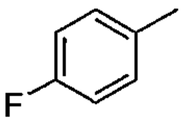
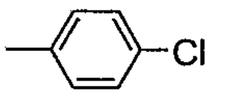
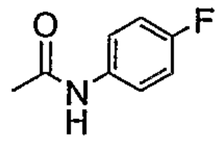
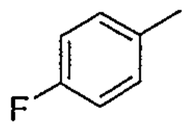
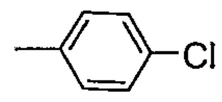
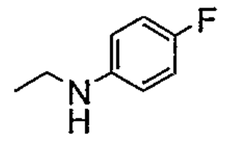
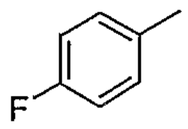
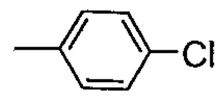
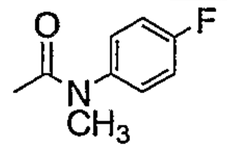
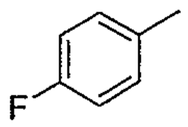
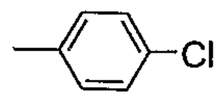
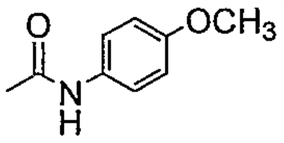
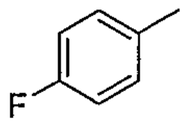
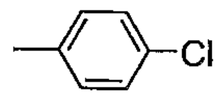
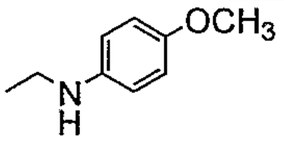
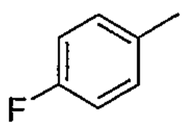
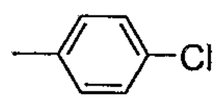
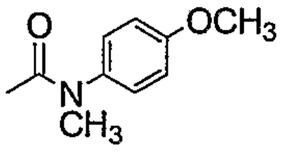
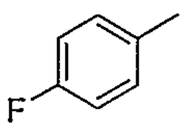
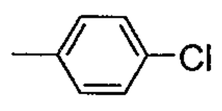
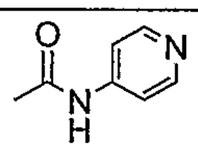
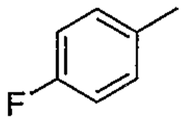
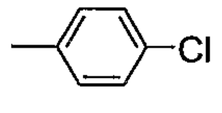
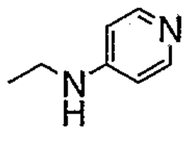
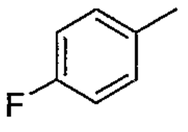
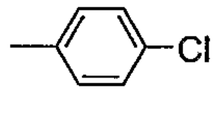
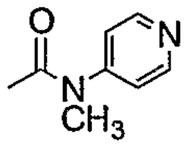
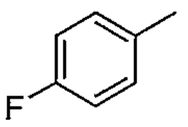
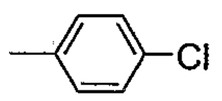
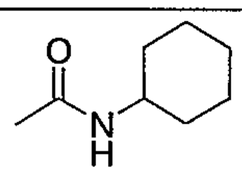
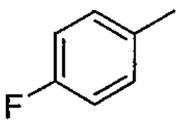
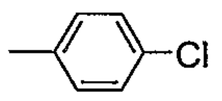
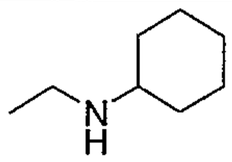
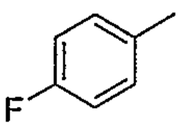
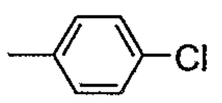
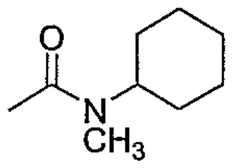
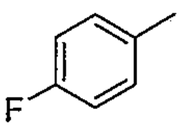
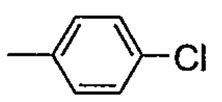
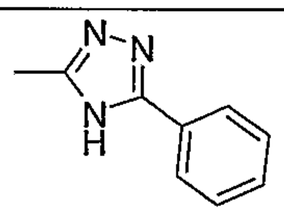
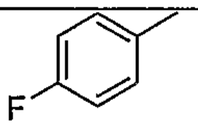
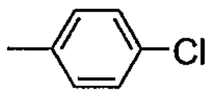
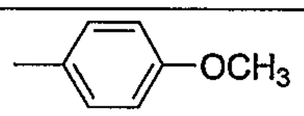
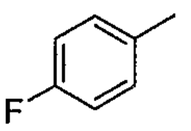
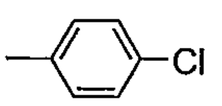
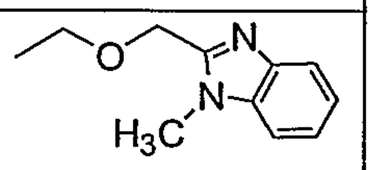
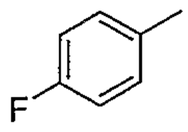
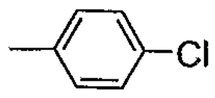
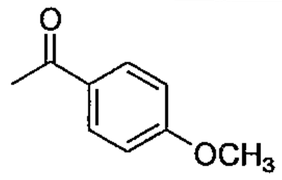
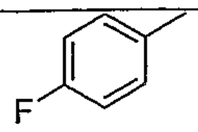
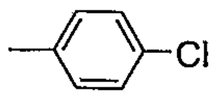
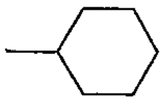
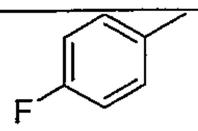
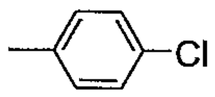
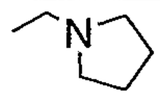
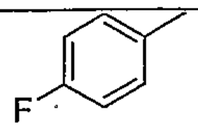
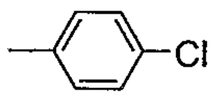
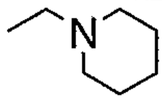
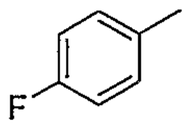
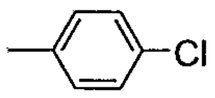
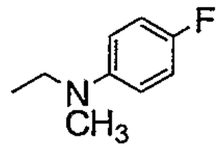
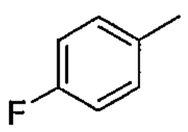
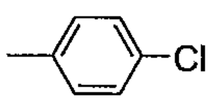
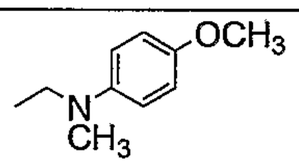
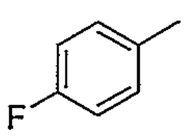
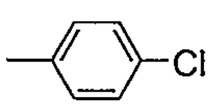
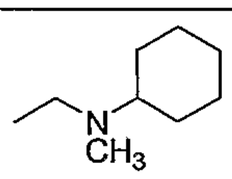
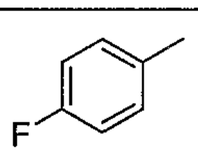
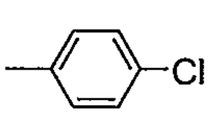
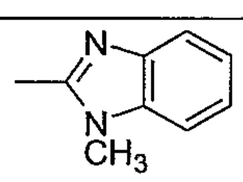
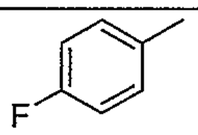
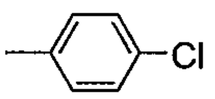
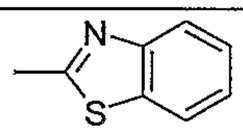
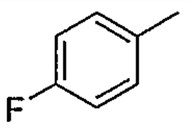
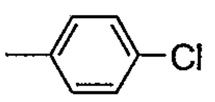
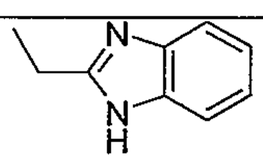
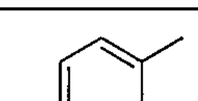
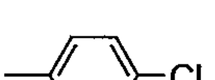
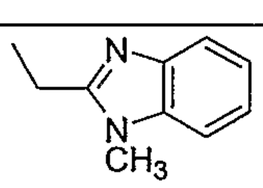
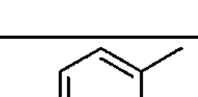
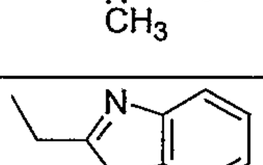
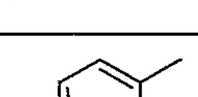
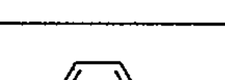
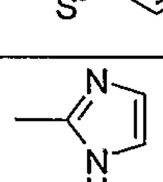
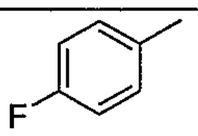
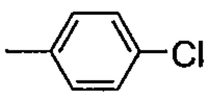
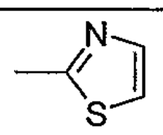
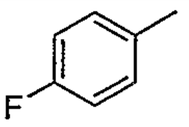
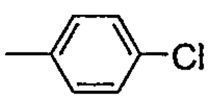
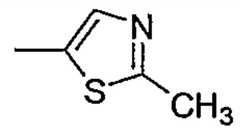
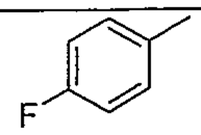
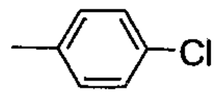
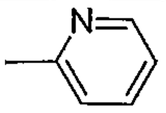
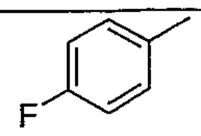
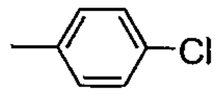
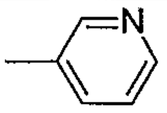
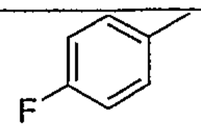
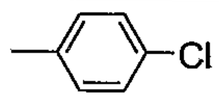
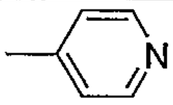
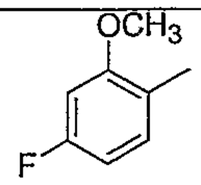
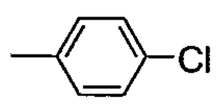
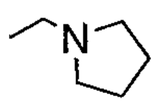
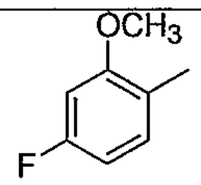
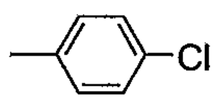
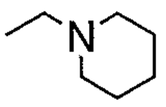
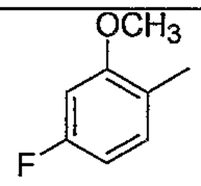
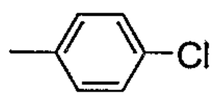
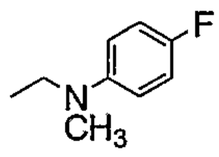
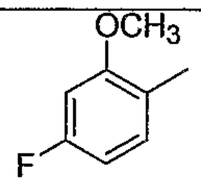
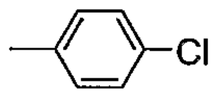
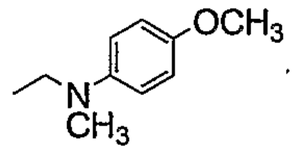
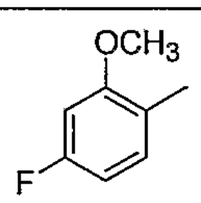
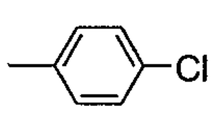
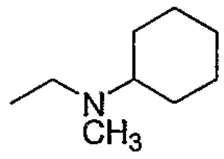
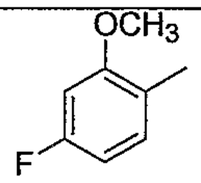
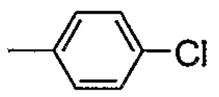
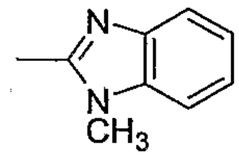
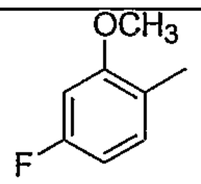
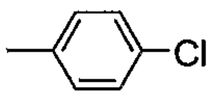
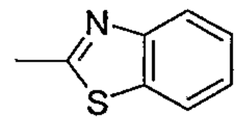
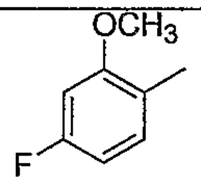
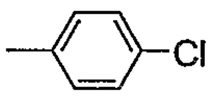
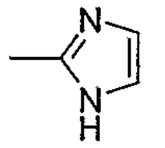
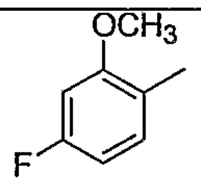
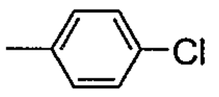
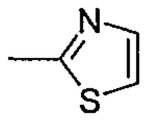
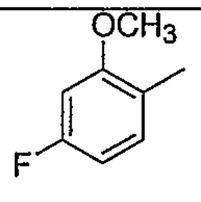
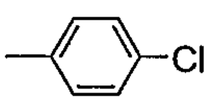
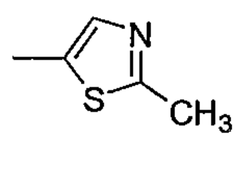
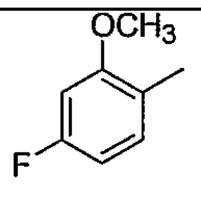
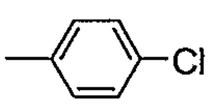
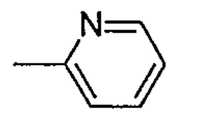
D227			
D228			

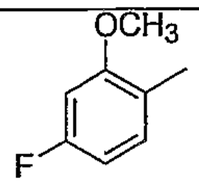
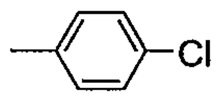
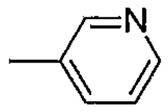
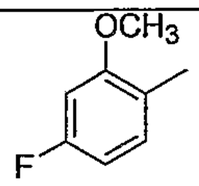
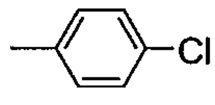
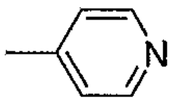
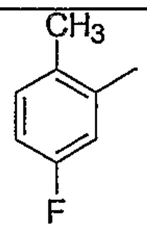
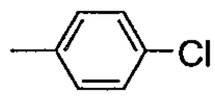
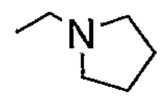
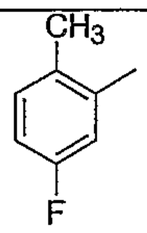
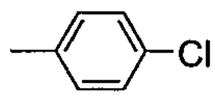
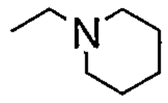
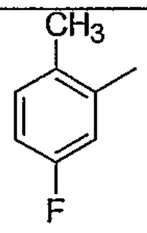
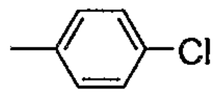
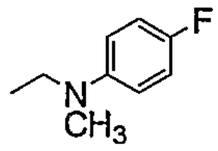
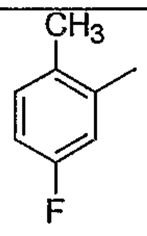
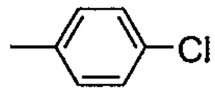
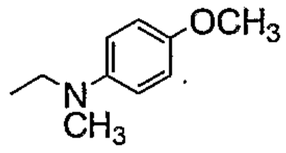
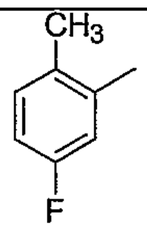
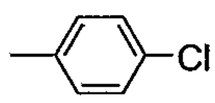
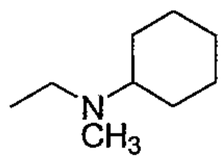
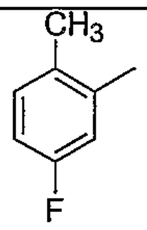
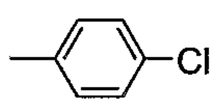
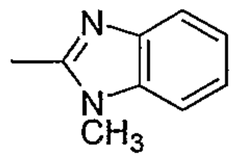
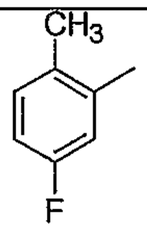
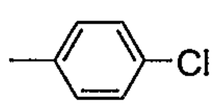
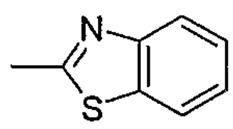
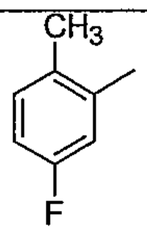
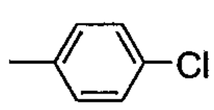
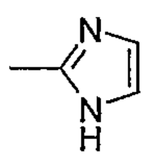
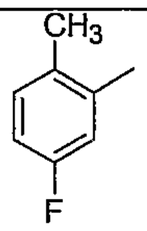
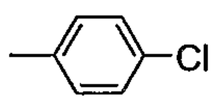
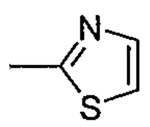
D229			
D230			
D231			
D232			
D233			
D234			
D235			
D236			
D237			
D238			
D239			
D240			
D241			

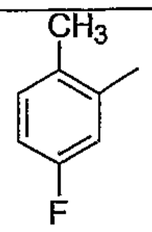
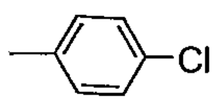
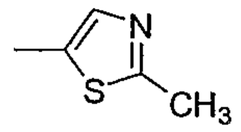
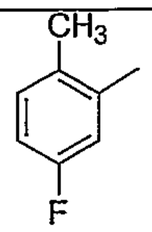
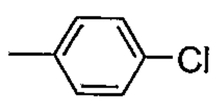
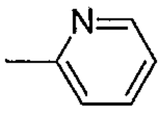
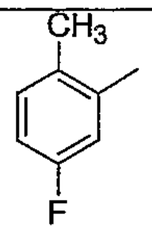
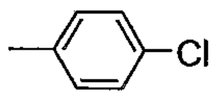
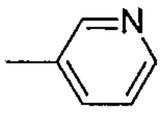
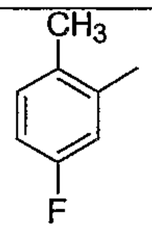
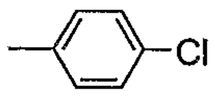
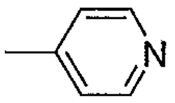
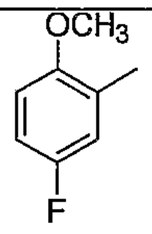
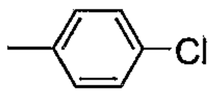
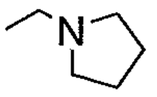
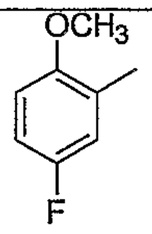
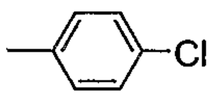
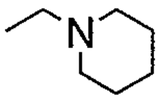
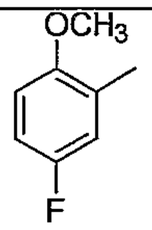
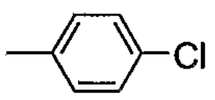
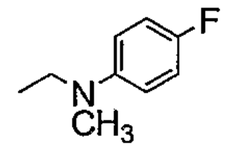
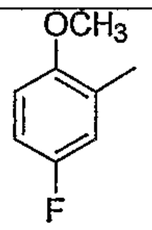
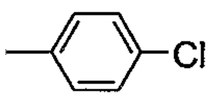
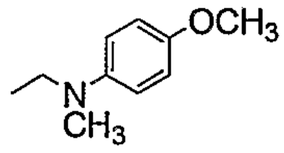
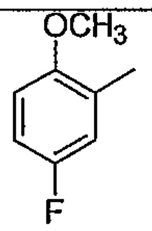
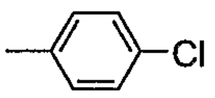
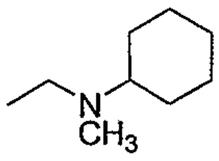
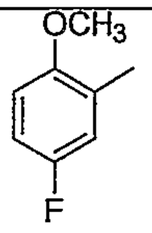
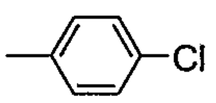
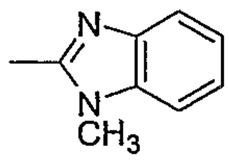
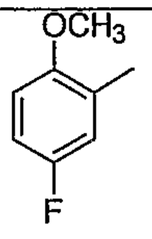
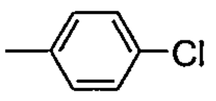
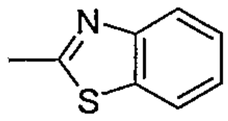
D242			
D243			
D244			
D245			
D246			
D247			
D248			
D249			
D250			
D251			
D252			
D253			
D254			
D255			

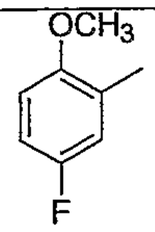
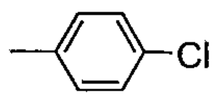
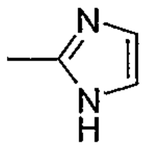
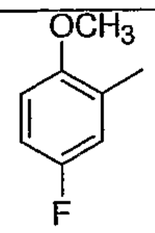
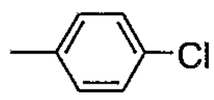
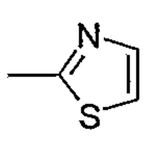
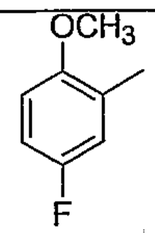
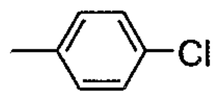
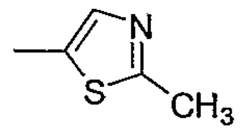
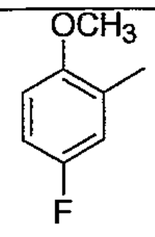
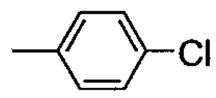
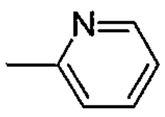
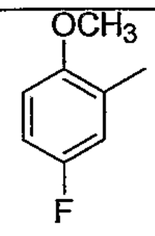
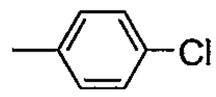
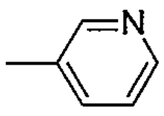
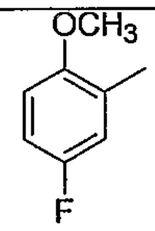
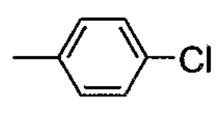
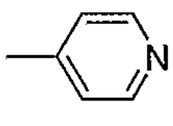
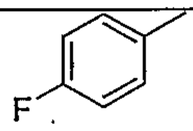
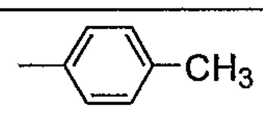
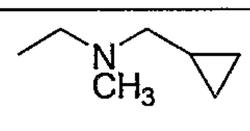
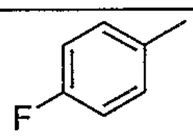
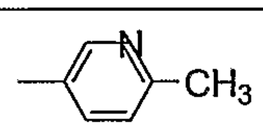
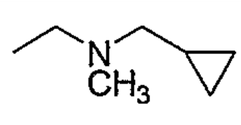
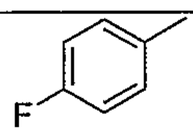
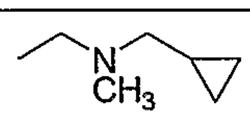
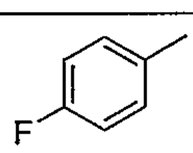
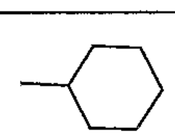
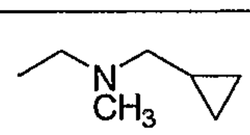
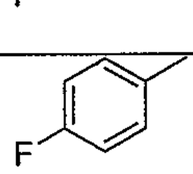
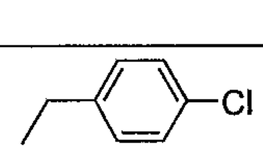
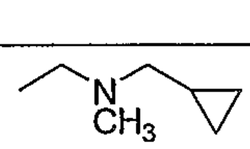
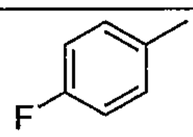
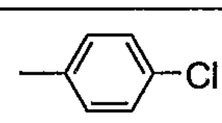
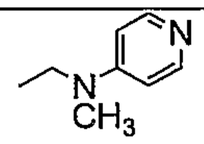
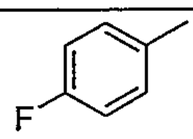
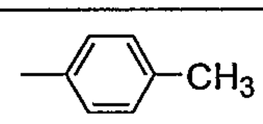
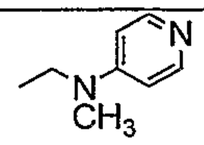
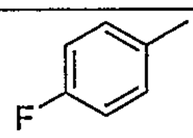
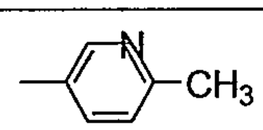
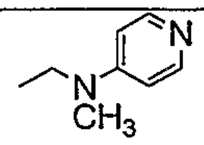
D256			
D257			
D258			
D259			
D260			
D261			
D262			
D263			
D264			
D265			
D266			
D267			
D268			
D269			

D270			
D271			
D272			
D273			
D274			
D275			
D276			
D277			
D278			
D279			
D280			
D281			
D282			
D283			
D284			

D285			
D286			
D287			
D288			
D289			
D290			
D291			
D292			
D293			
D294			
D295			
D296			
D297			
D298			

D299			
D300			
D301			
D302			
D303			
D304			
D305			
D306			
D307			
D308			
D309			

D310			
D311			
D312			
D313			
D314			
D315			
D316			
D317			
D318			
D319			
D320			

D321			
D322			
D323			
D324			
D325			
D326			
D327			
D328			
D329		CH_3	
D330			
D331			
D332			
D333			
D334			

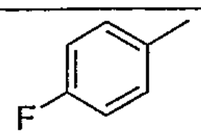
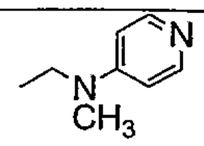
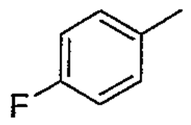
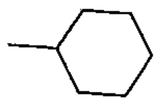
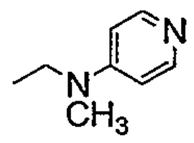
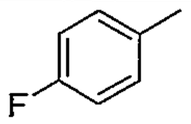
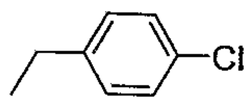
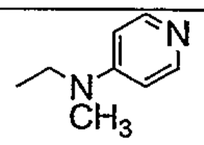
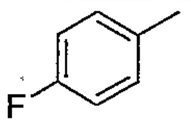
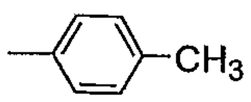
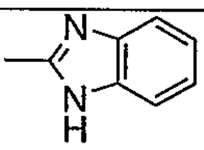
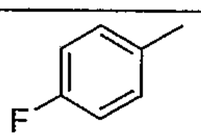
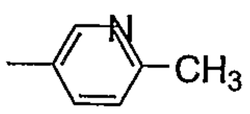
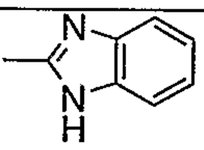
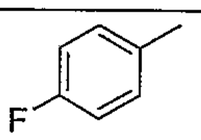
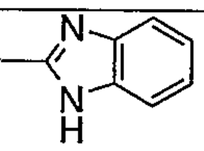
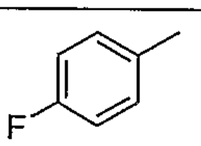
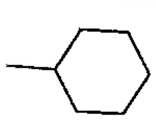
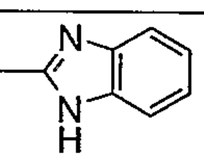
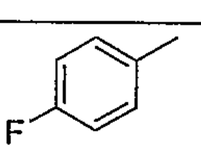
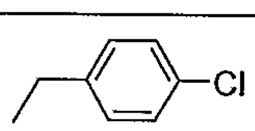
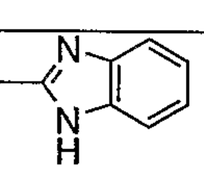
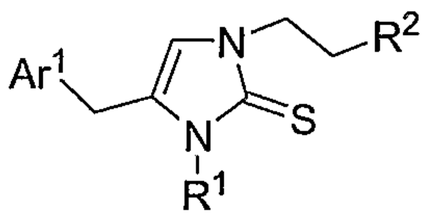
D335		CH_3	
D336			
D337			
D338			
D339			
D340		CH_3	
D341			
D342			

TABLE D-4



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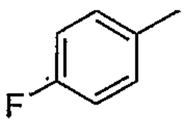
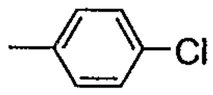
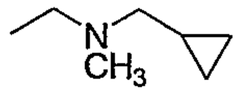
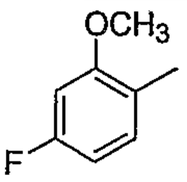
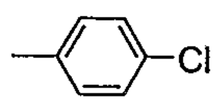
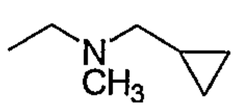
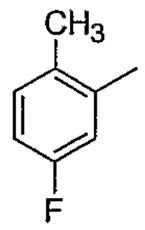
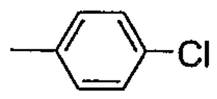
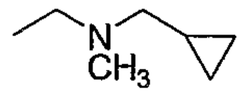
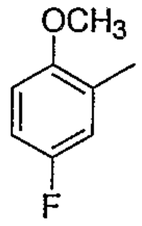
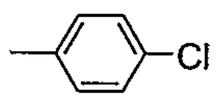
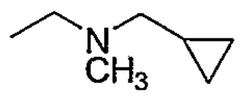
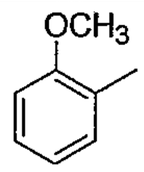
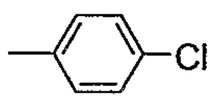
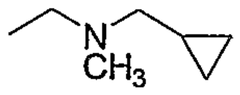
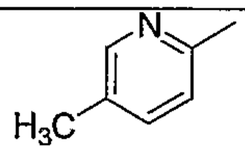
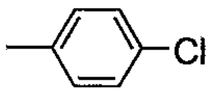
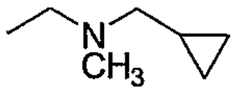
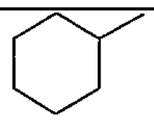
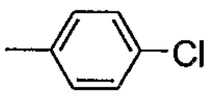
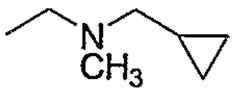
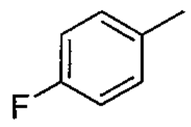
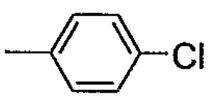
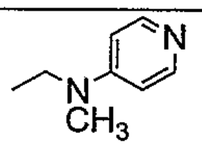
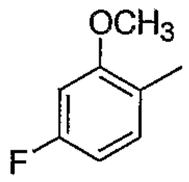
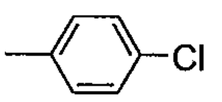
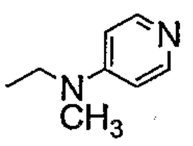
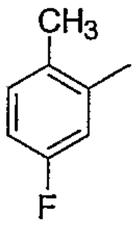
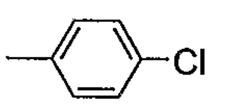
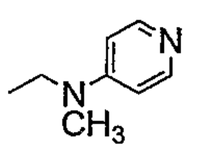
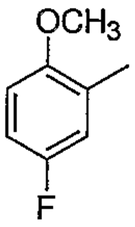
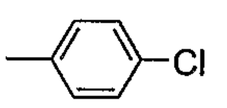
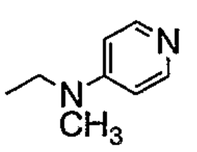
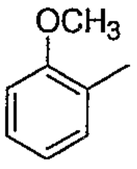
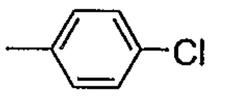
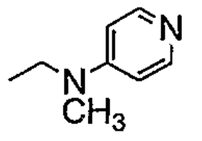
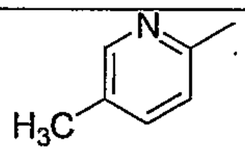
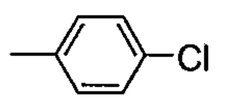
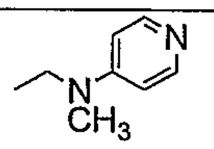
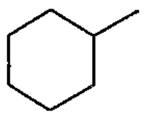
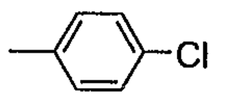
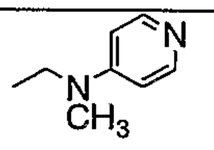
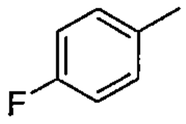
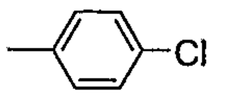
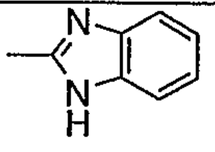
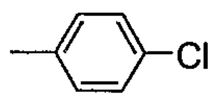
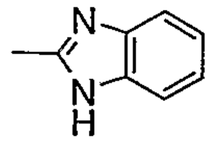
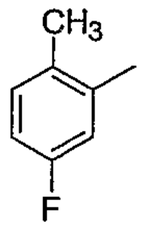
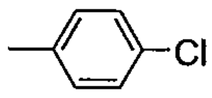
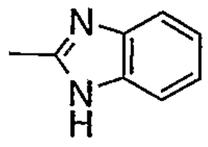
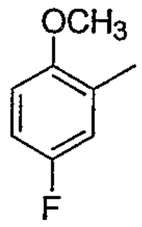
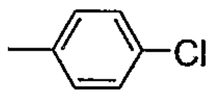
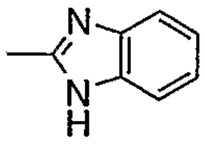
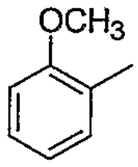
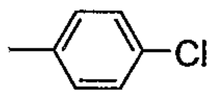
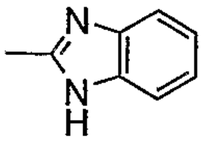
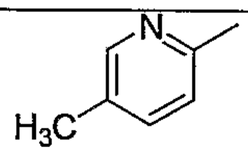
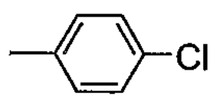
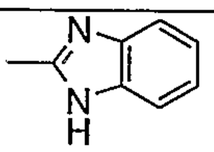
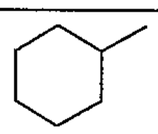
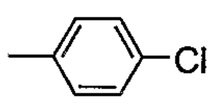
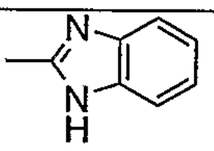
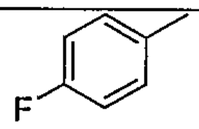
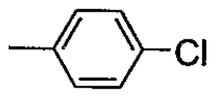
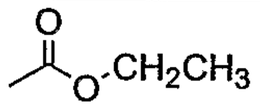
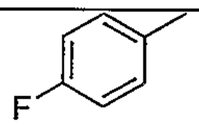
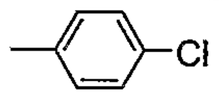
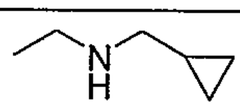
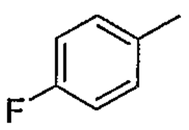
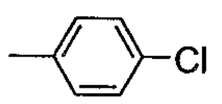
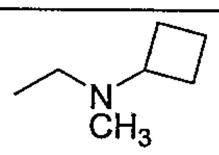
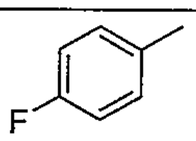
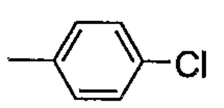
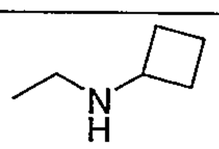
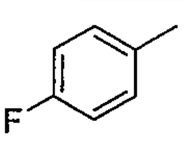
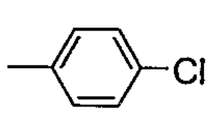
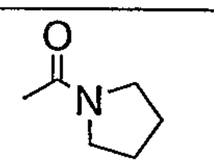
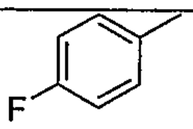
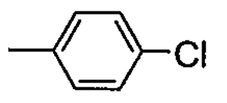
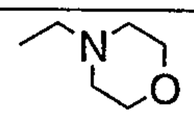
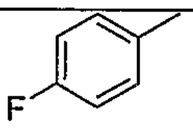
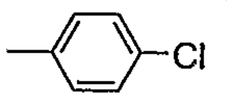
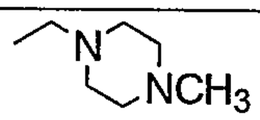
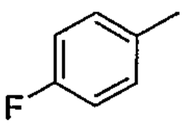
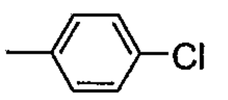
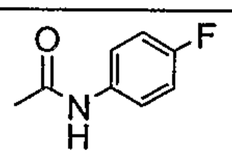
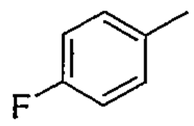
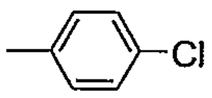
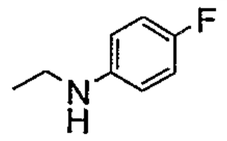
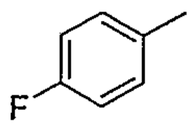
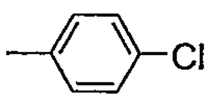
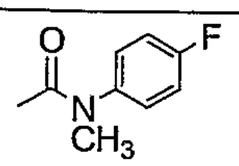
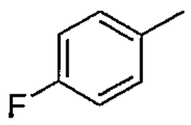
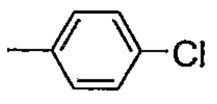
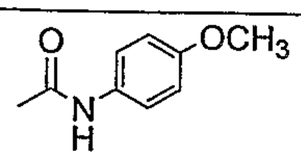
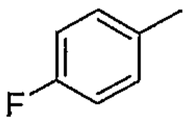
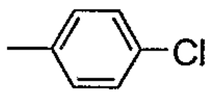
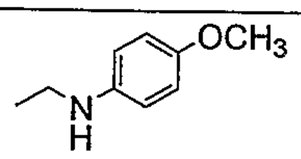
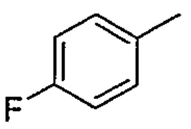
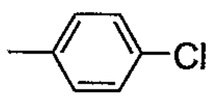
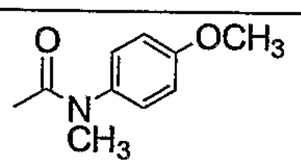
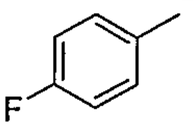
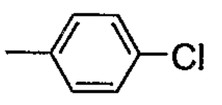
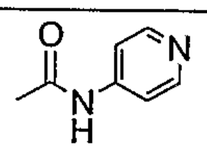
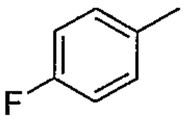
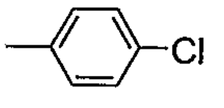
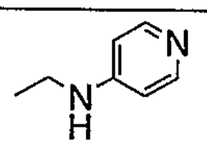
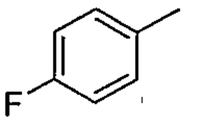
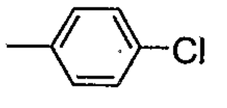
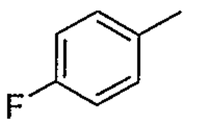
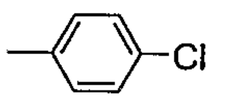
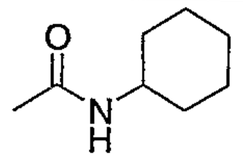
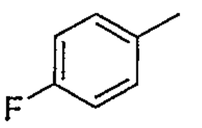
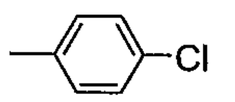
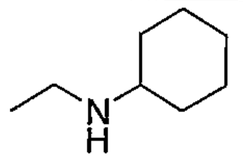
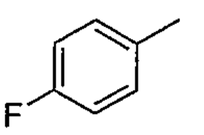
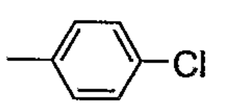
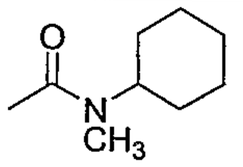
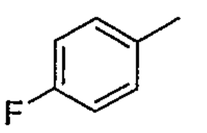
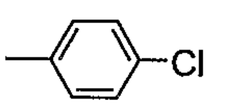
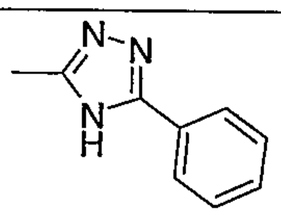
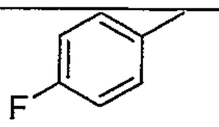
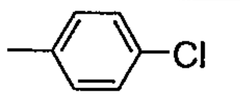
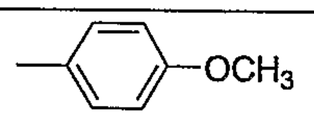
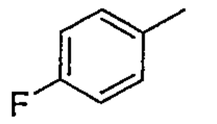
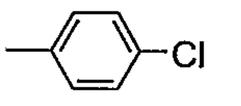
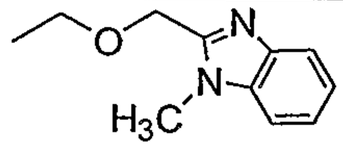
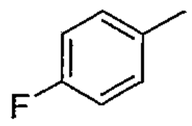
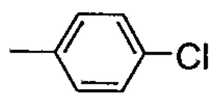
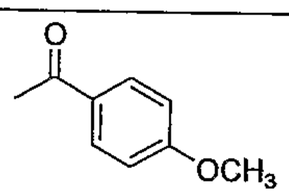
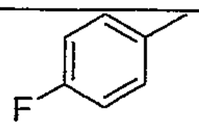
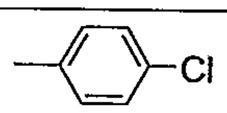
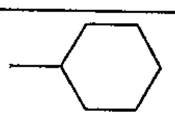
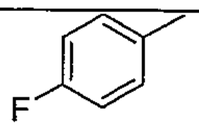
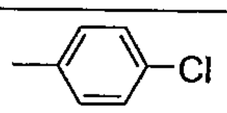
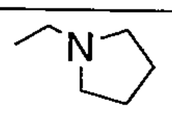
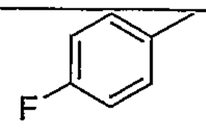
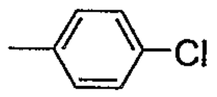
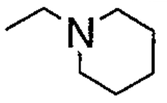
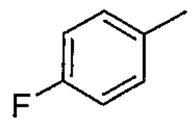
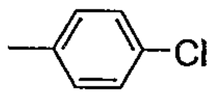
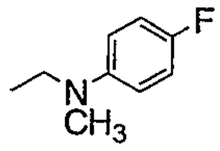
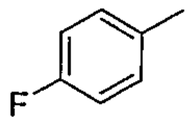
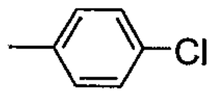
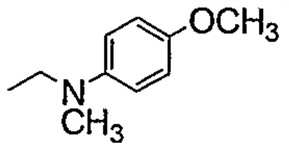
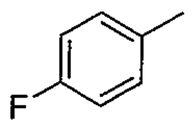
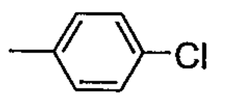
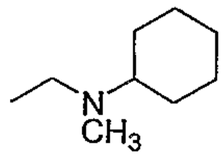
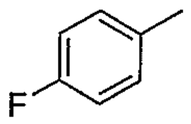
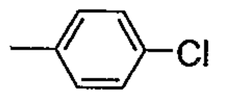
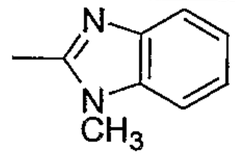
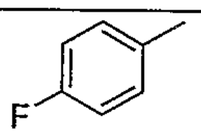
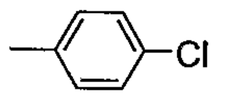
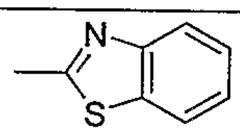
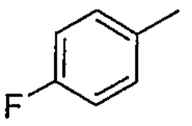
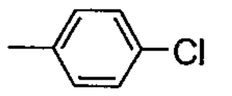
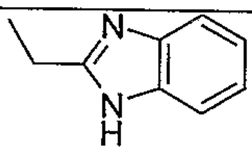
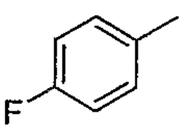
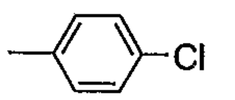
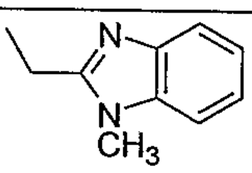
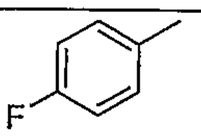
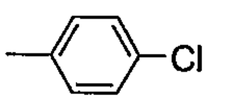
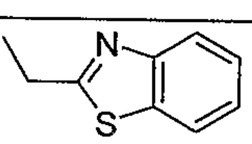
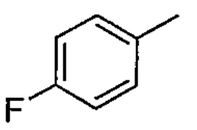
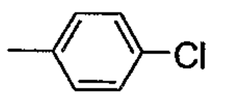
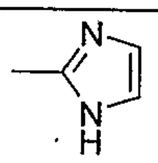
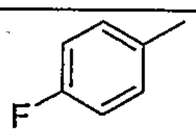
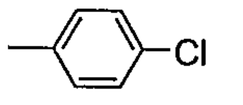
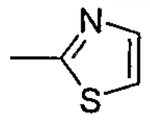
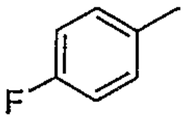
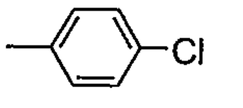
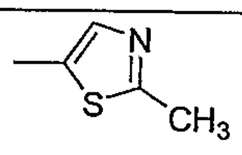
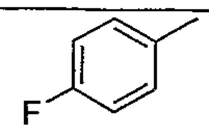
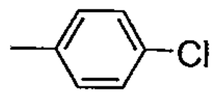
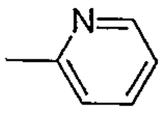
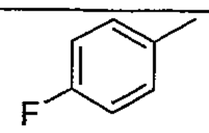
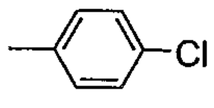
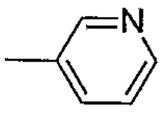
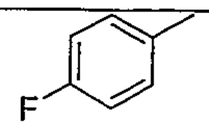
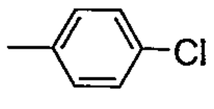
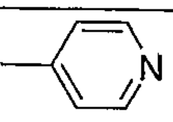
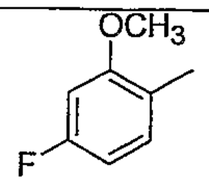
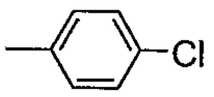
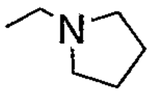
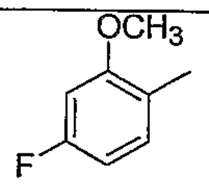
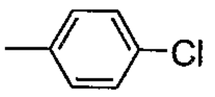
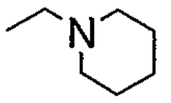
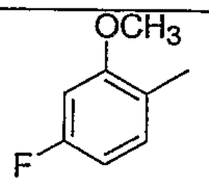
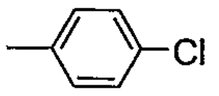
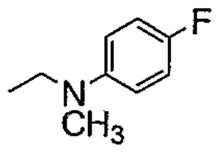
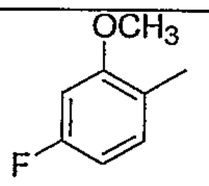
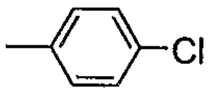
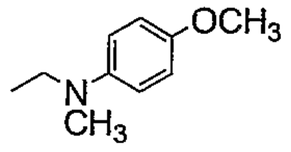
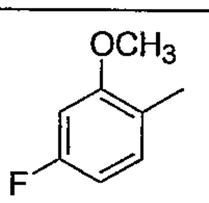
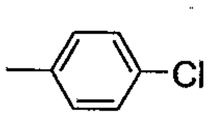
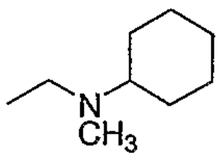
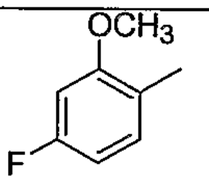
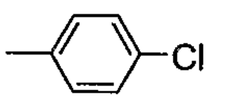
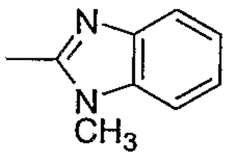
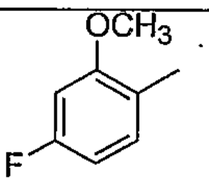
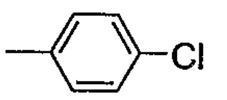
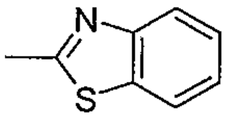
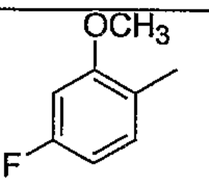
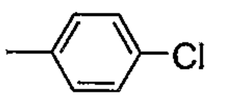
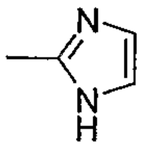
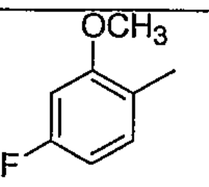
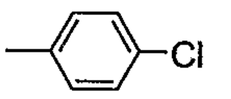
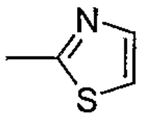
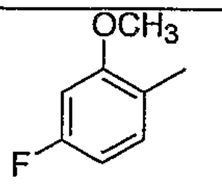
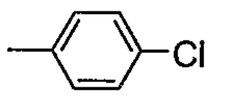
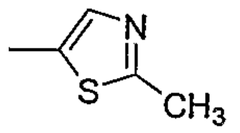
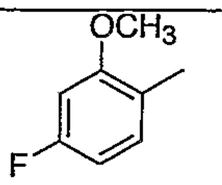
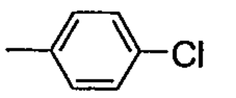
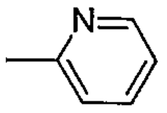
D343			
D344			

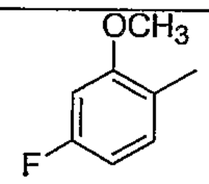
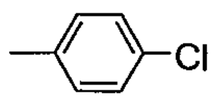
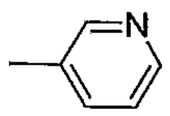
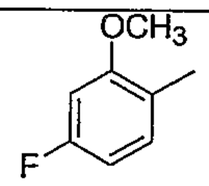
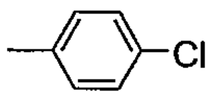
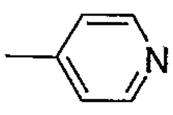
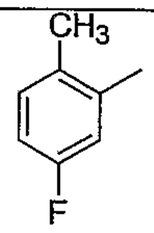
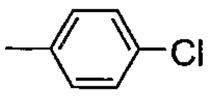
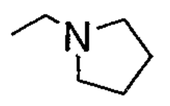
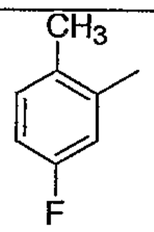
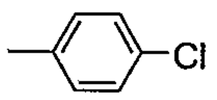
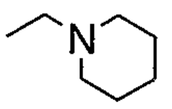
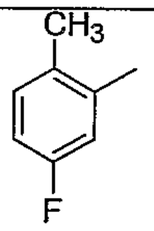
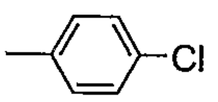
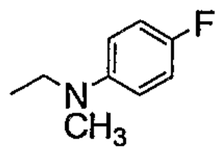
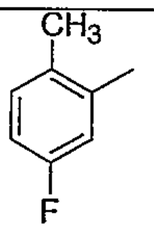
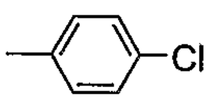
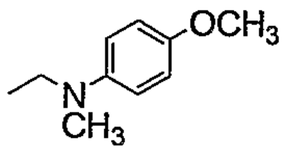
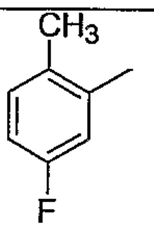
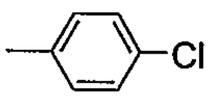
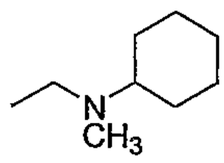
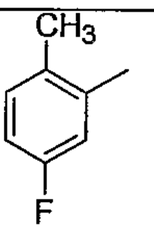
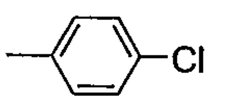
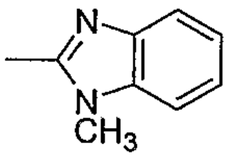
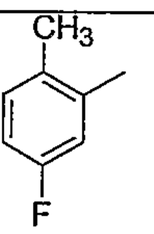
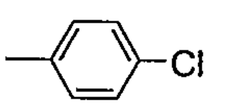
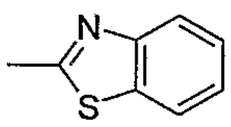
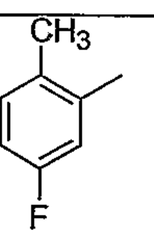
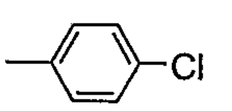
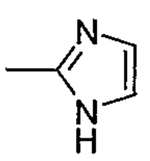
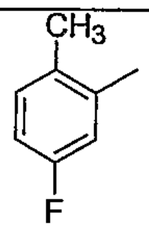
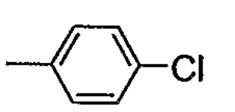
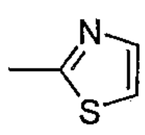
D345			
D346			
D347			
D348			
D349			
D350			
D351			
D352			
D353			
D354			
D355			
D356			
D357			

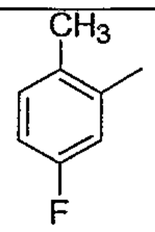
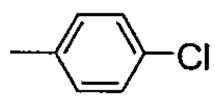
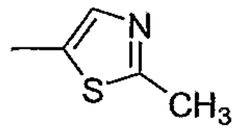
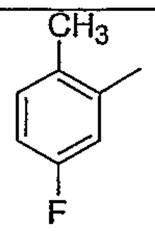
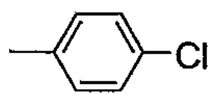
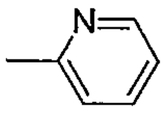
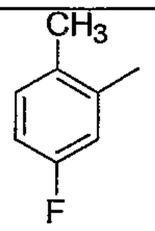
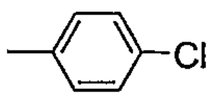
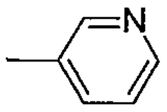
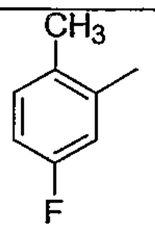
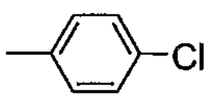
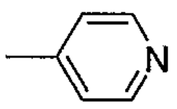
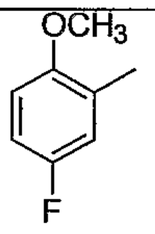
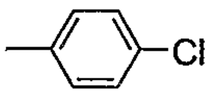
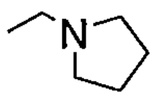
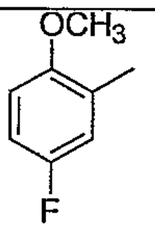
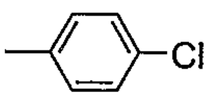
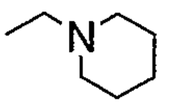
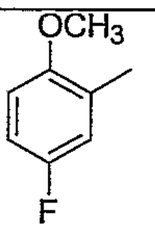
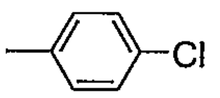
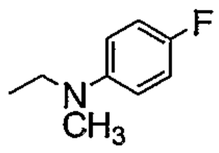
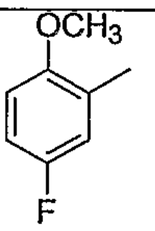
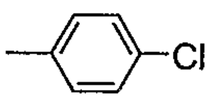
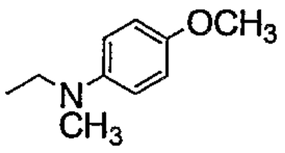
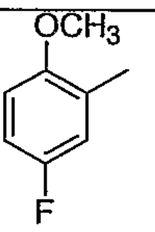
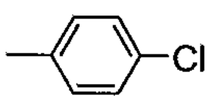
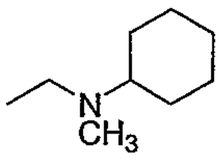
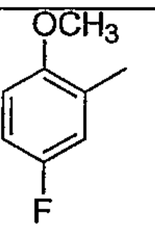
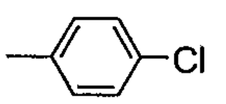
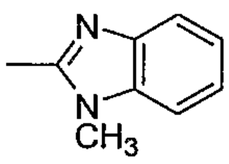
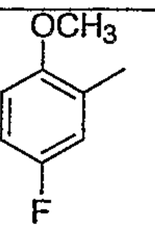
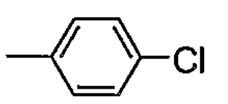
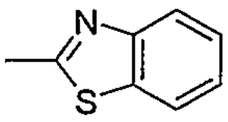
D358			
D359			
D360			
D361			
D362			
D363			
D364			
D365			
D366			
D367			
D368			
D369			
D370			
D371			

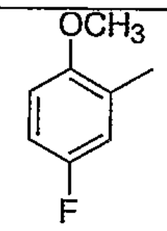
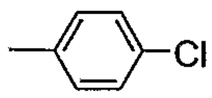
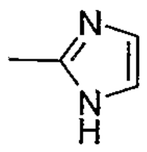
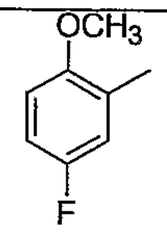
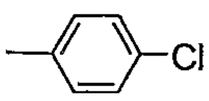
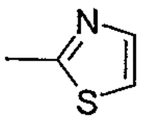
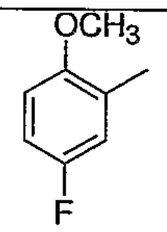
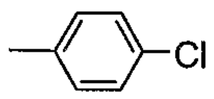
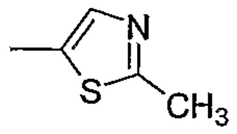
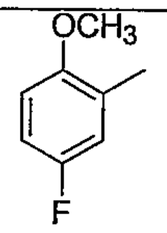
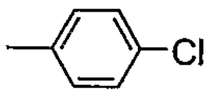
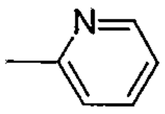
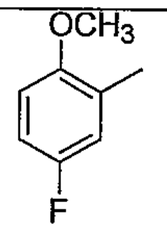
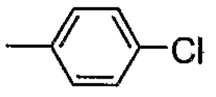
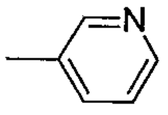
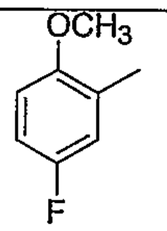
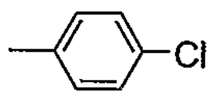
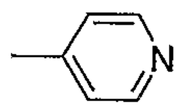
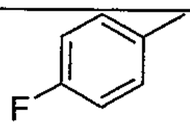
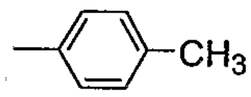
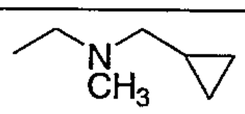
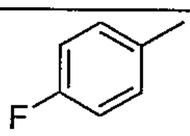
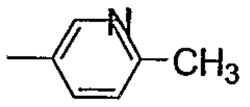
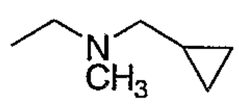
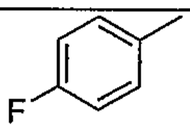
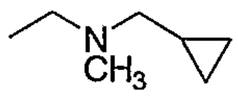
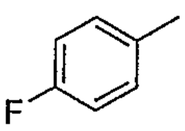
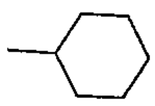
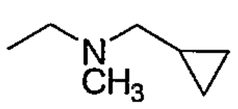
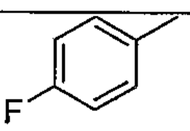
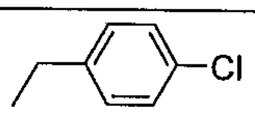
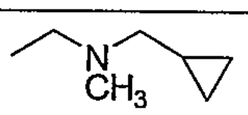
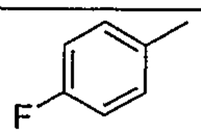
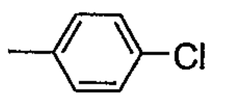
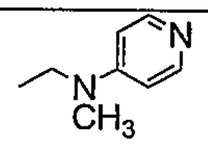
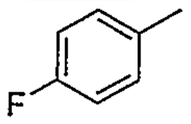
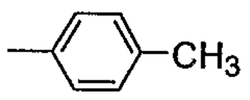
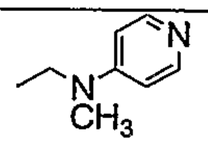
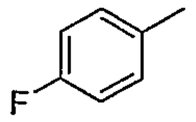
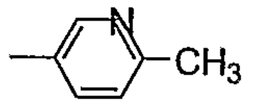
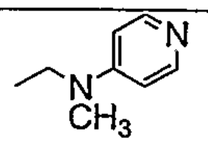
D372			
D373			
D374			
D375			
D376			
D377			
D378			
D379			
D380			
D381			
D382			
D383			
D384			
D385			

D386			
D387			
D388			
D389			
D390			
D391			
D392			
D393			
D394			
D395			
D396			
D397			
D398			
D399			
D400			

D401			
D402			
D403			
D404			
D405			
D406			
D407			
D408			
D409			
D410			
D411			
D412			
D413			
D414			

D415			
D416			
D417			
D418			
D419			
D420			
D421			
D422			
D423			
D424			
D425			

D426			
D427			
D428			
D429			
D430			
D431			
D432			
D433			
D434			
D435			
D436			

D437			
D438			
D439			
D440			
D441			
D442			
D443			
D444			
D445		CH_3	
D446			
D447			
D448			
D449			
D450			

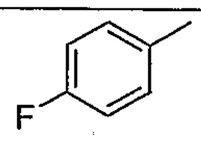
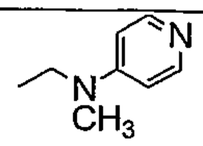
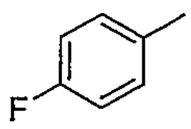
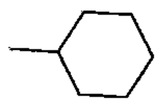
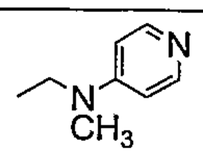
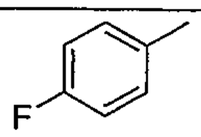
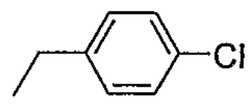
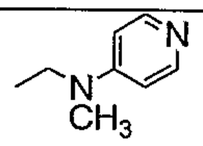
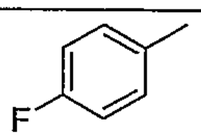
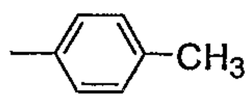
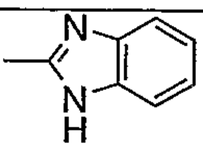
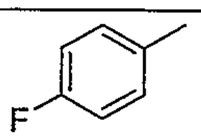
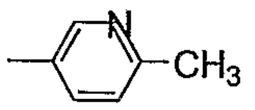
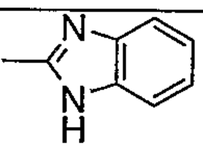
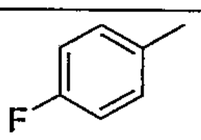
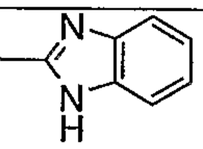
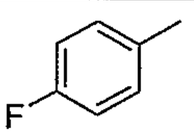
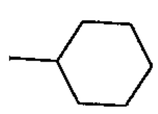
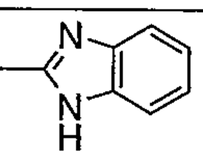
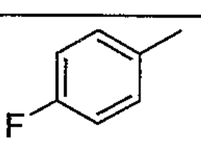
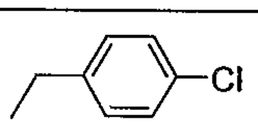
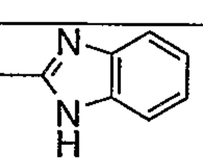
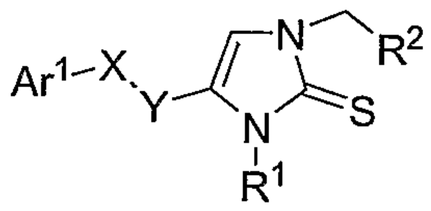
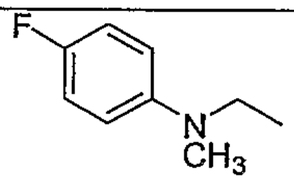
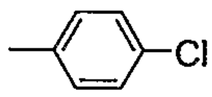
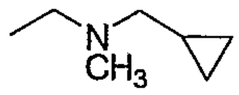
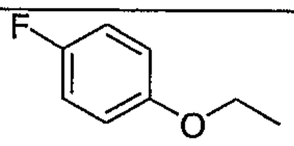
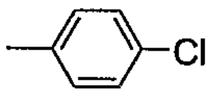
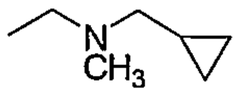
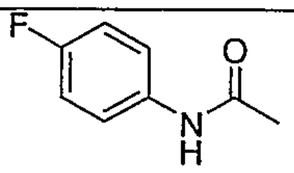
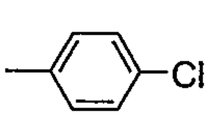
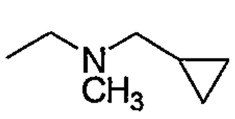
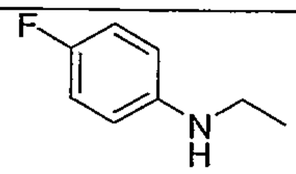
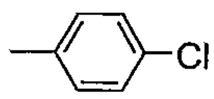
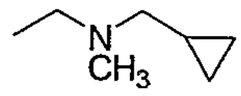
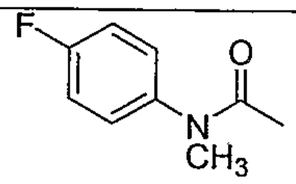
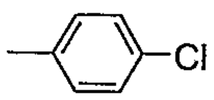
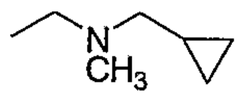
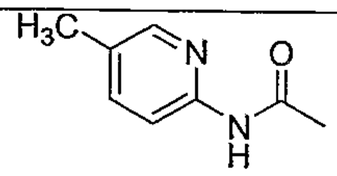
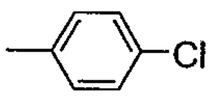
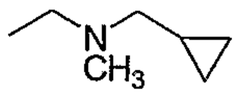
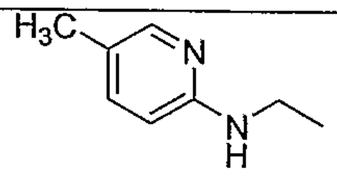
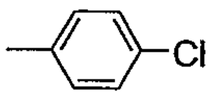
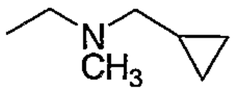
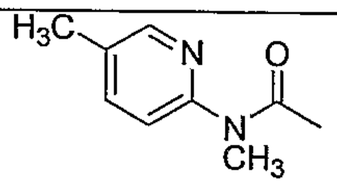
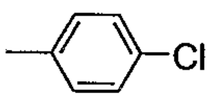
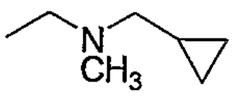
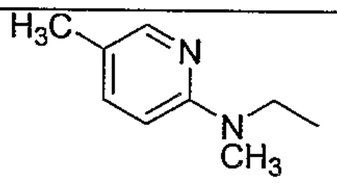
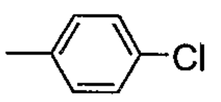
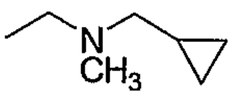
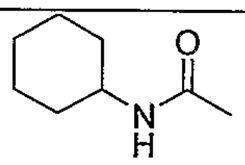
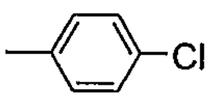
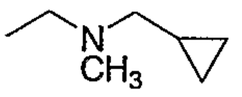
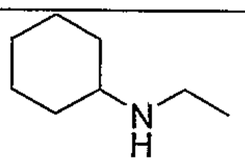
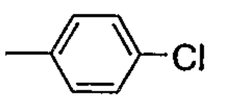
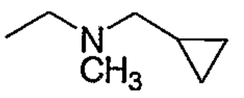
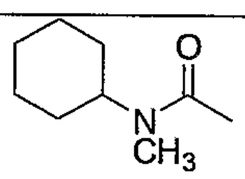
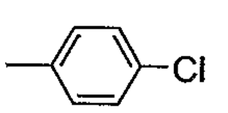
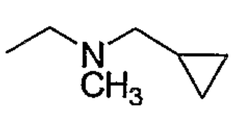
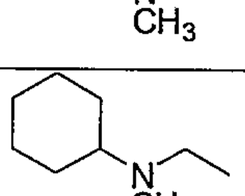
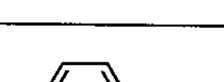
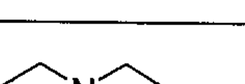
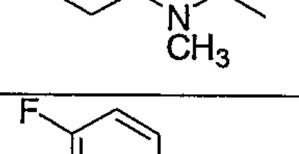
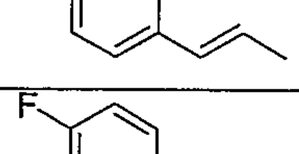
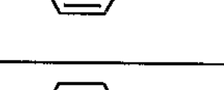
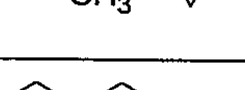
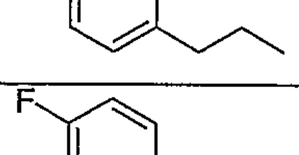
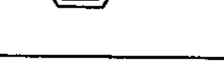
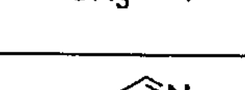
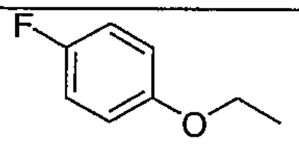
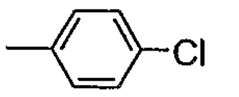
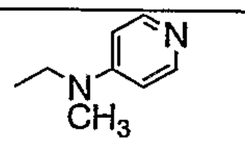
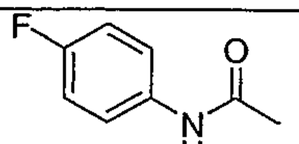
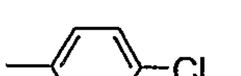
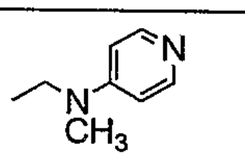
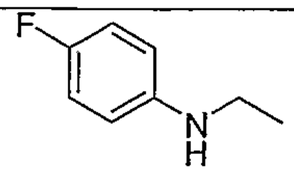
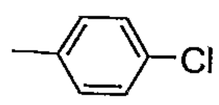
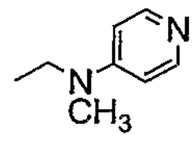
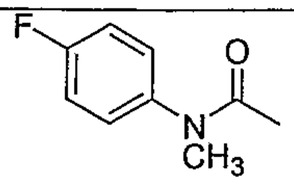
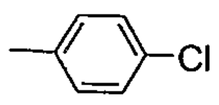
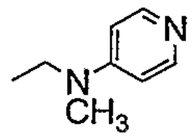
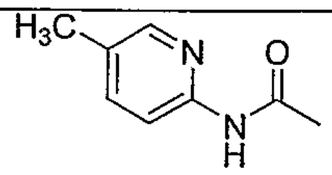
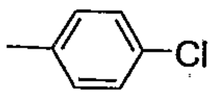
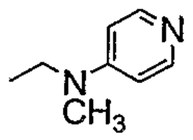
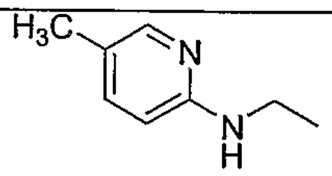
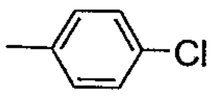
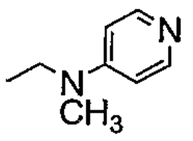
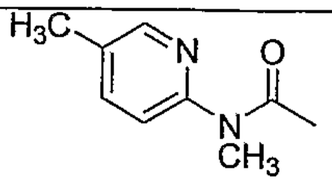
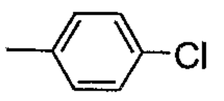
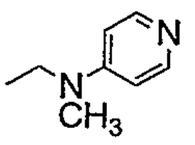
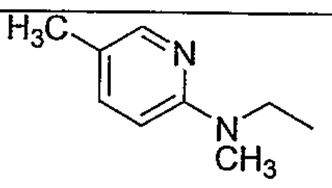
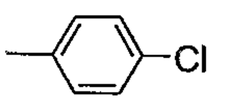
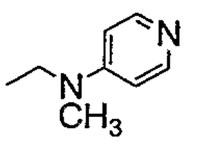
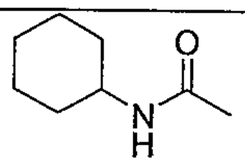
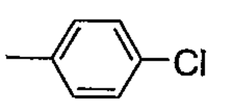
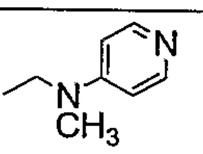
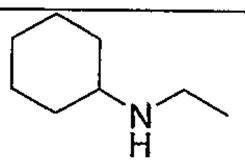
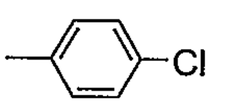
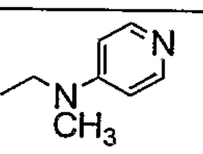
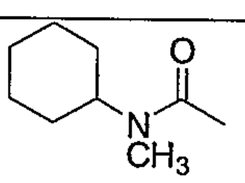
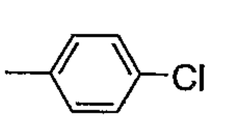
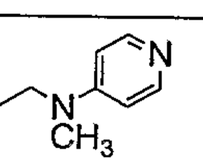
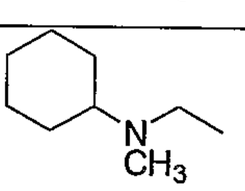
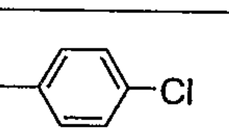
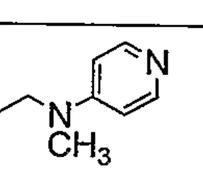
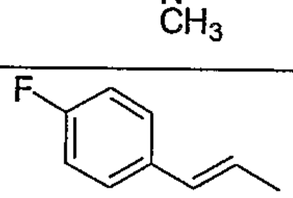
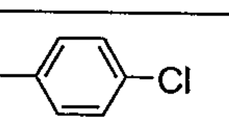
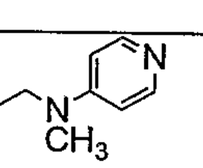
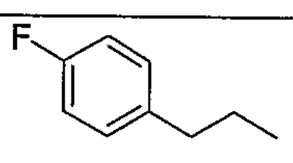
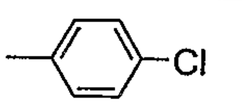
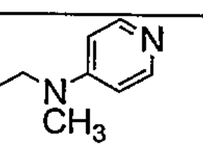
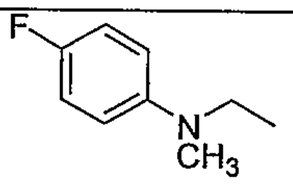
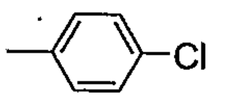
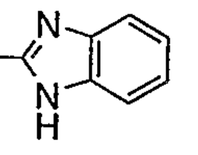
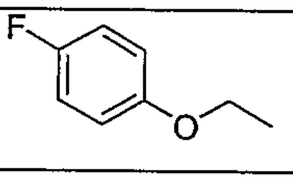
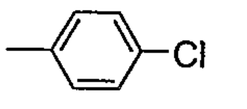
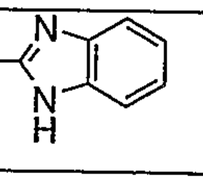
D451		CH_3	
D452			
D453			
D454			
D455			
D456		CH_3	
D457			
D458			

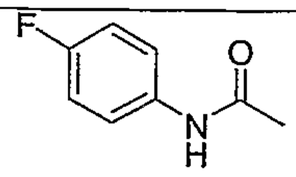
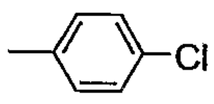
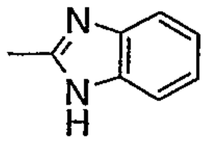
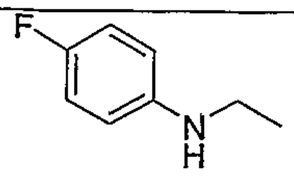
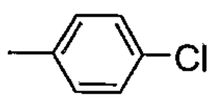
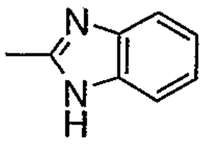
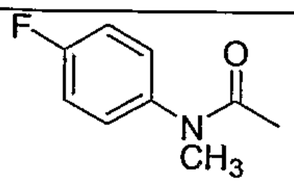
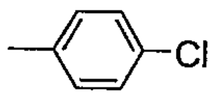
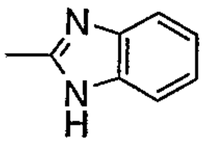
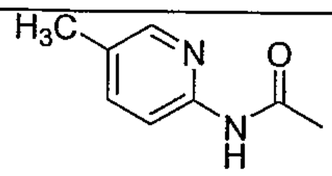
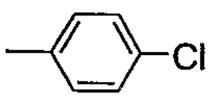
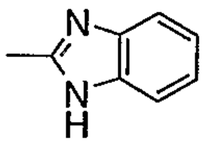
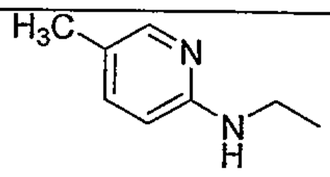
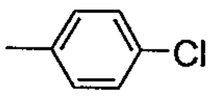
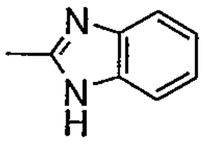
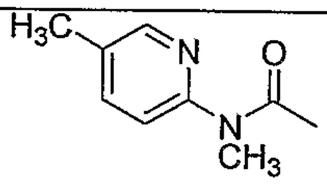
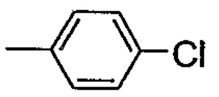
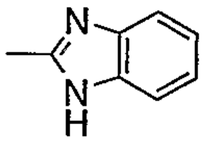
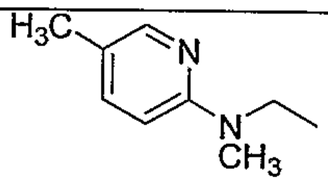
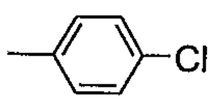
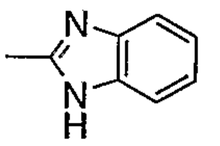
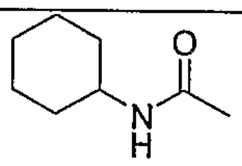
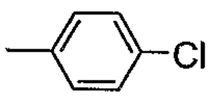
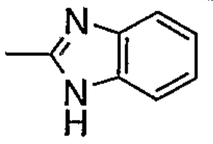
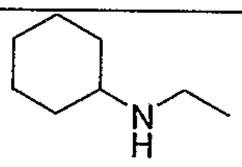
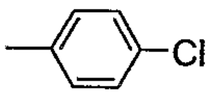
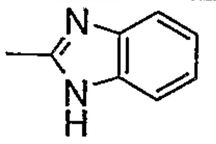
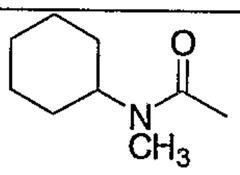
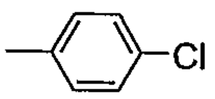
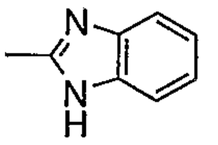
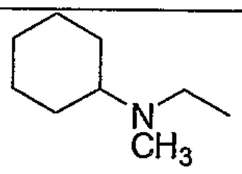
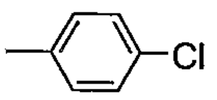
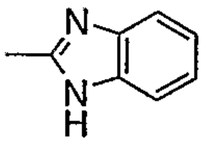
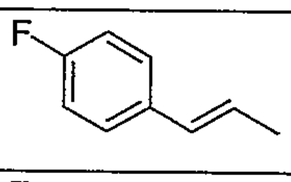
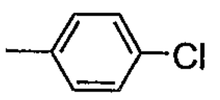
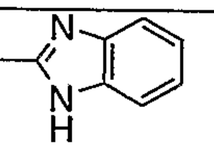
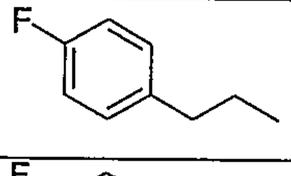
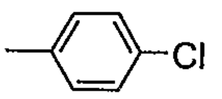
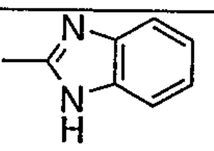
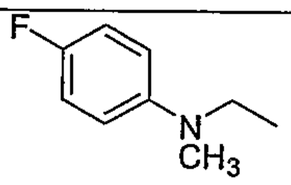
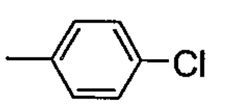
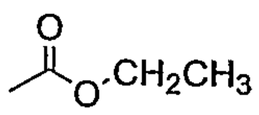
TABLE D-5

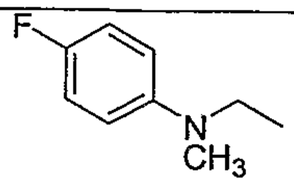
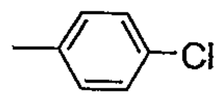
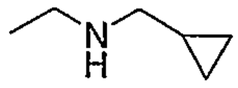
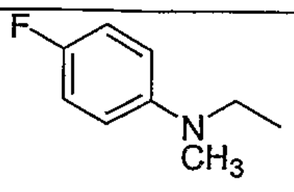
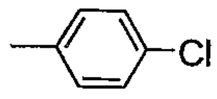
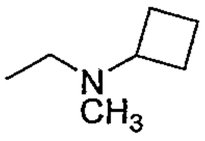
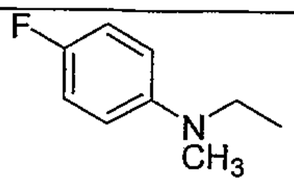
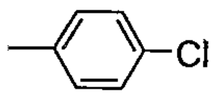
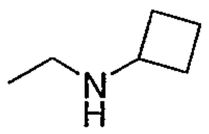
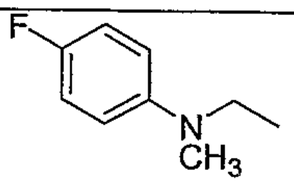
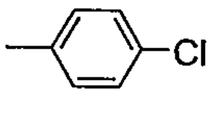
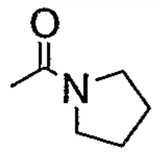
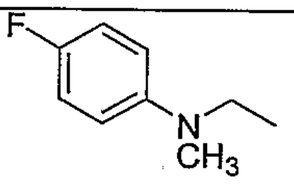
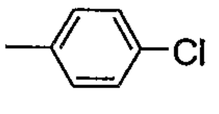
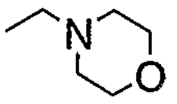
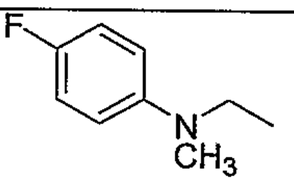
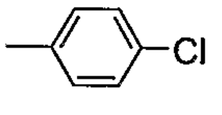
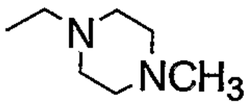
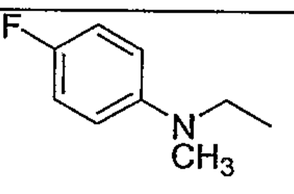
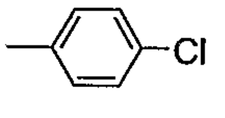
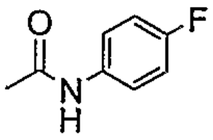
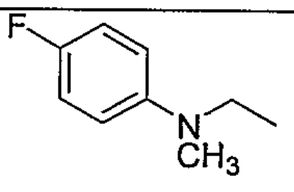
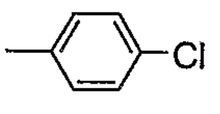
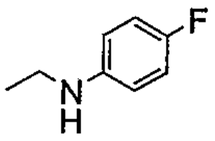
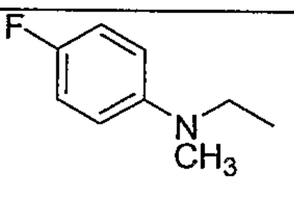
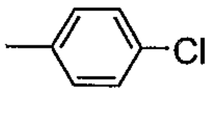
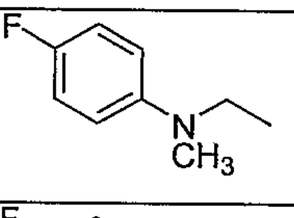
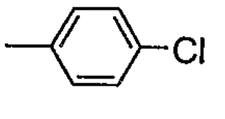
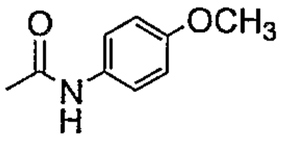
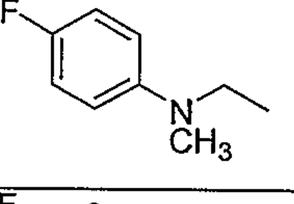
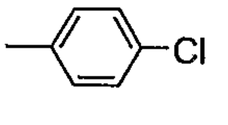
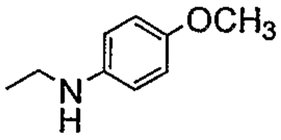
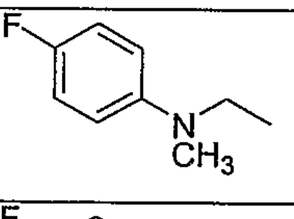
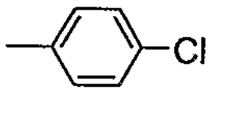
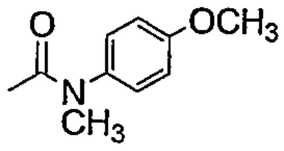
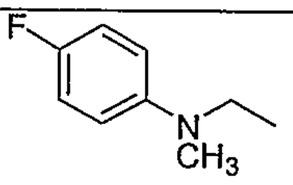
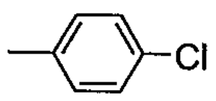
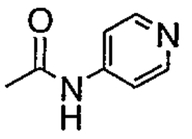


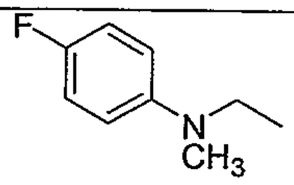
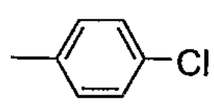
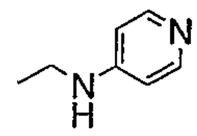
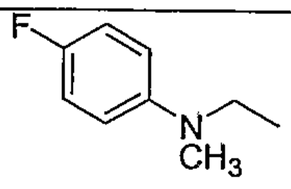
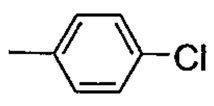
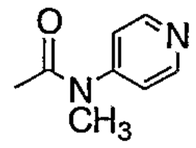
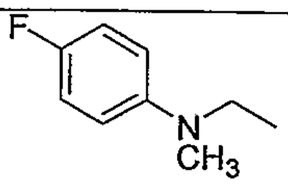
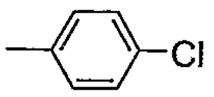
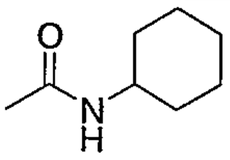
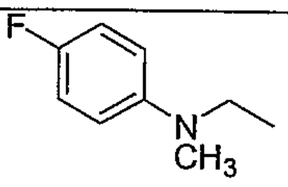
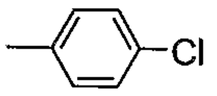
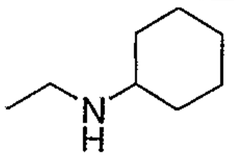
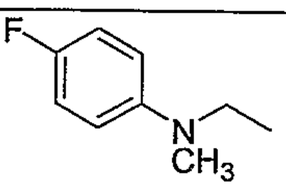
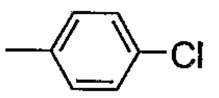
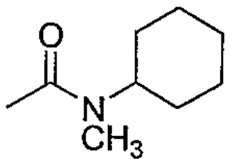
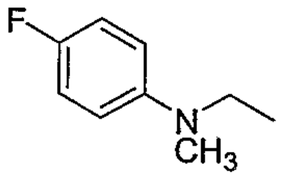
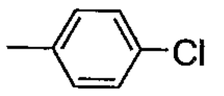
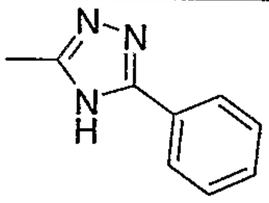
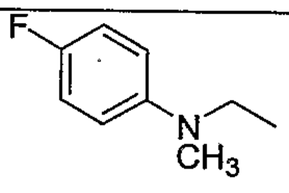
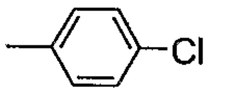
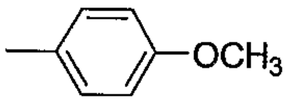
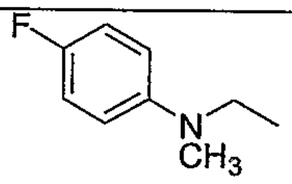
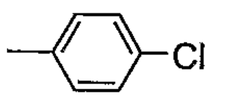
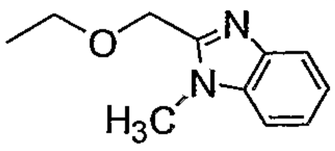
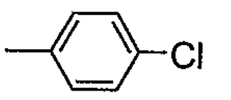
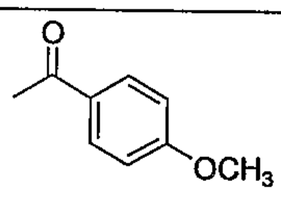
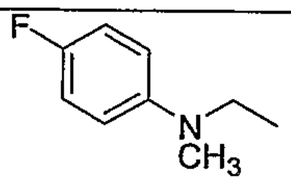
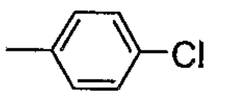
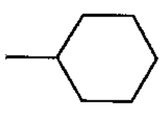
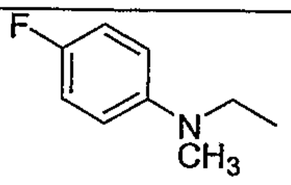
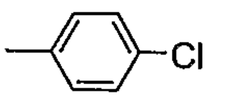
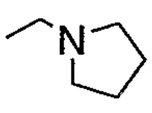
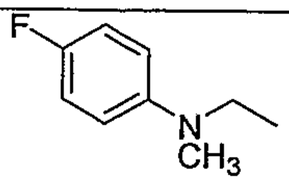
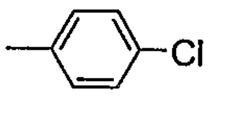
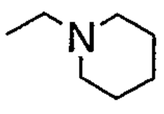
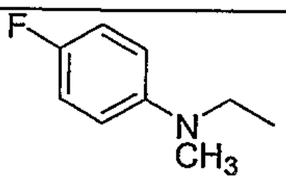
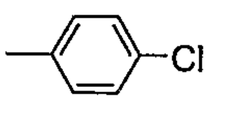
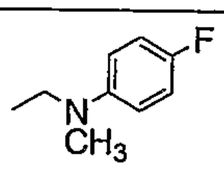
Cpd. No.	Ar^1-X-Y	R^1	R^2
D459			
D460			
D461			

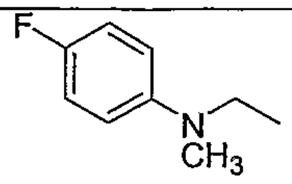
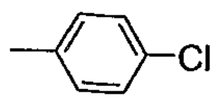
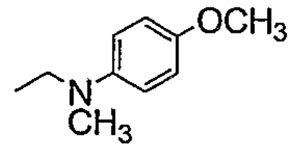
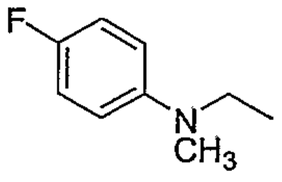
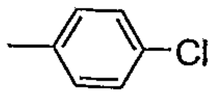
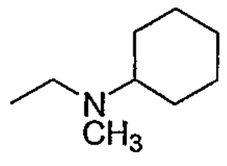
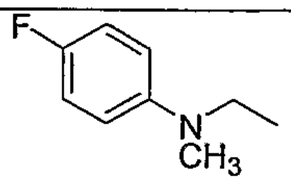
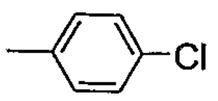
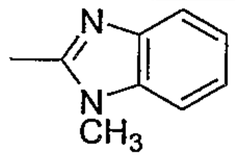
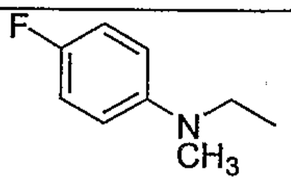
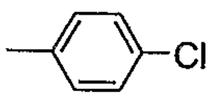
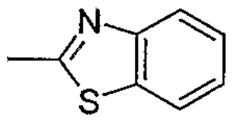
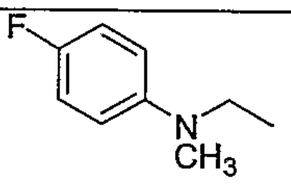
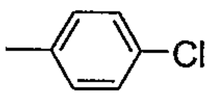
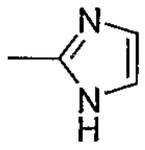
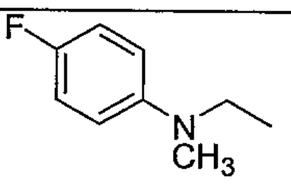
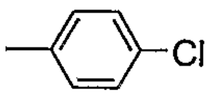
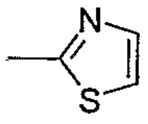
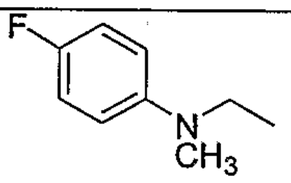
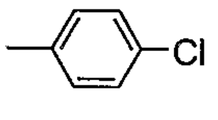
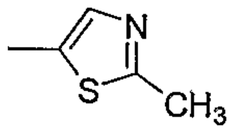
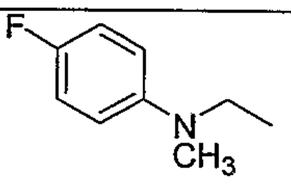
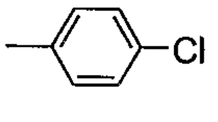
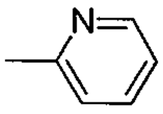
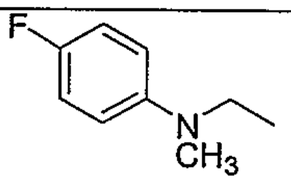
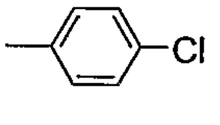
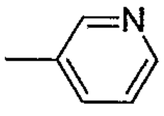
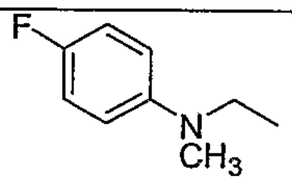
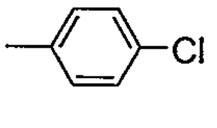
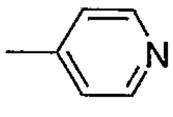
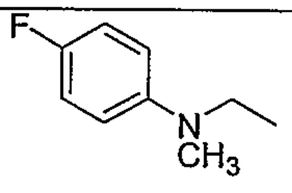
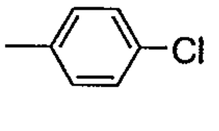
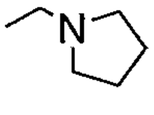
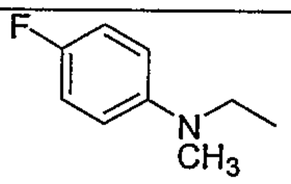
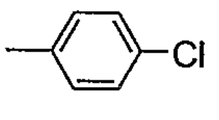
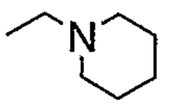
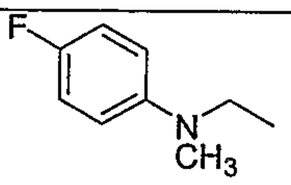
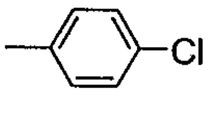
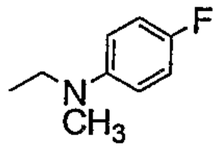
D462			
D463			
D464			
D465			
D466			
D467			
D468			
D469			
D470			
D471			
D472			
D473			
D474			
D475			
D476			

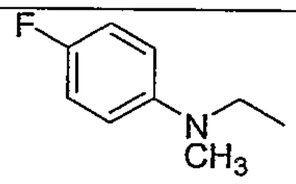
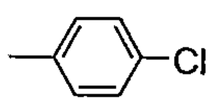
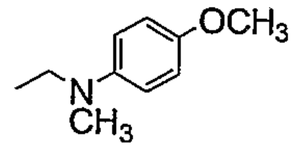
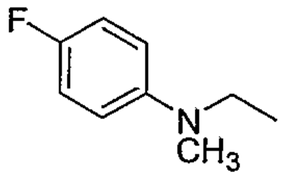
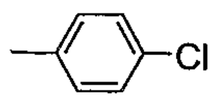
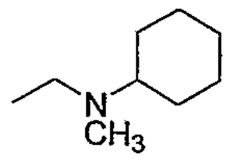
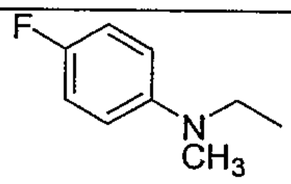
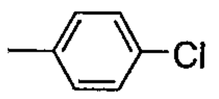
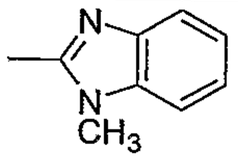
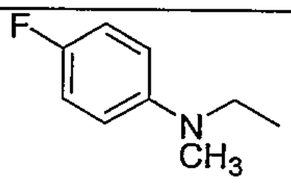
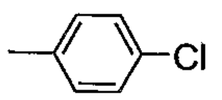
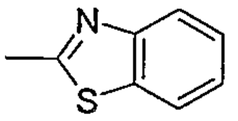
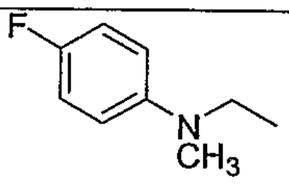
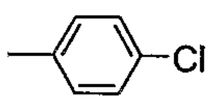
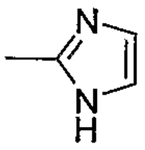
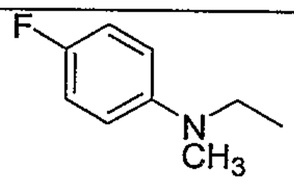
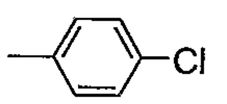
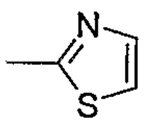
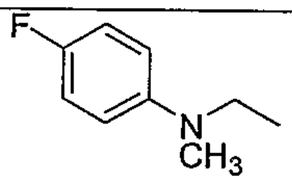
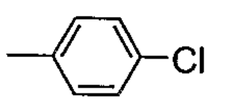
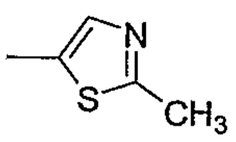
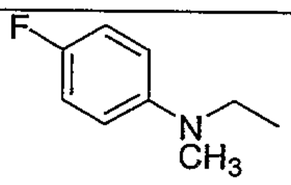
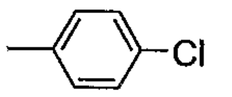
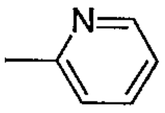
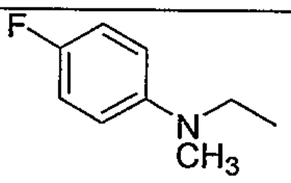
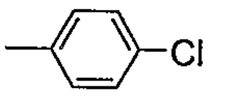
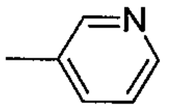
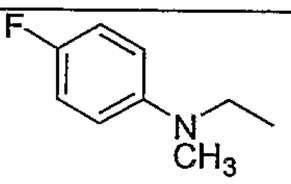
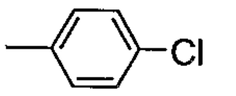
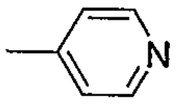
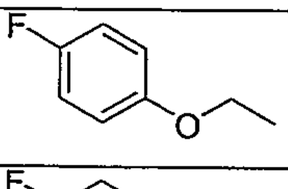
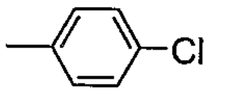
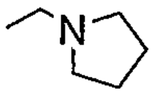
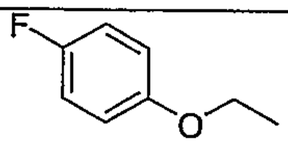
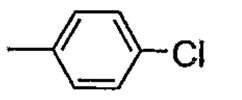
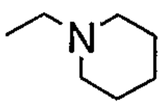
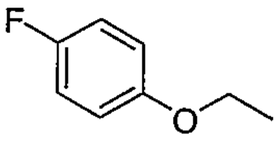
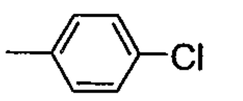
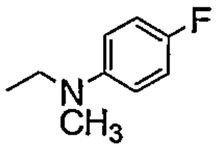
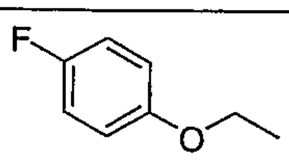
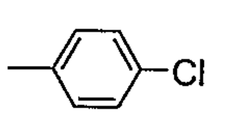
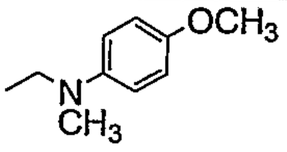
D477			
D478			
D479			
D480			
D481			
D482			
D483			
D484			
D485			
D486			
D487			
D488			
D489			
D490			

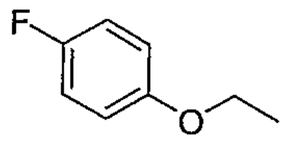
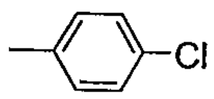
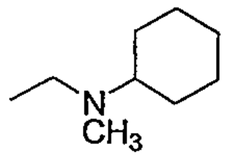
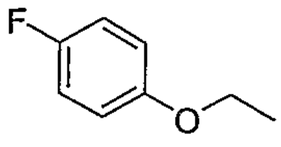
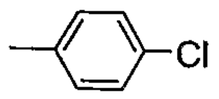
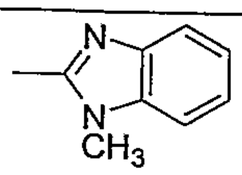
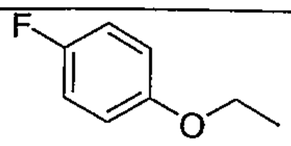
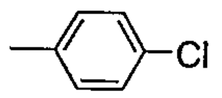
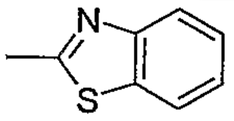
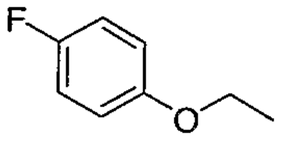
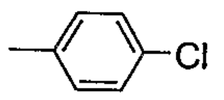
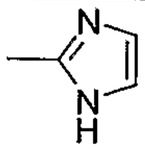
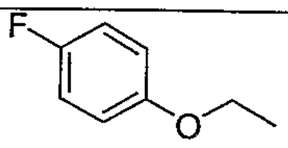
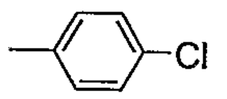
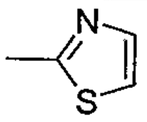
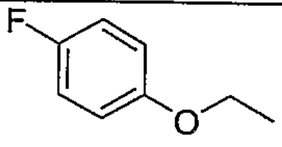
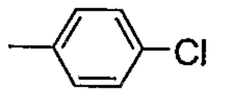
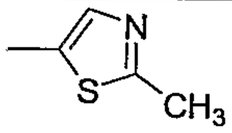
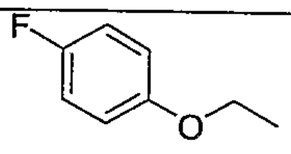
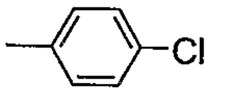
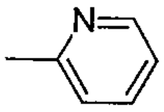
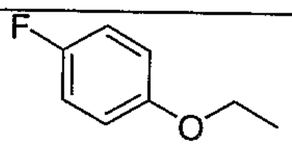
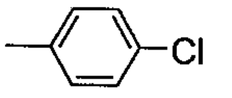
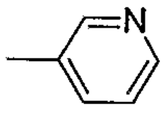
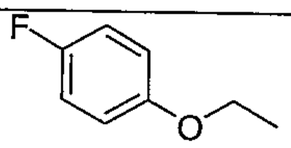
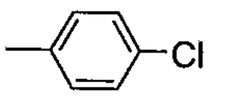
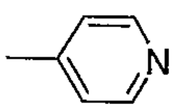
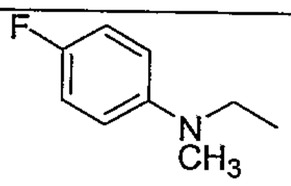
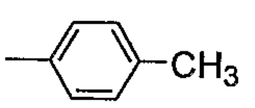
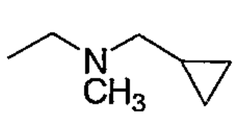
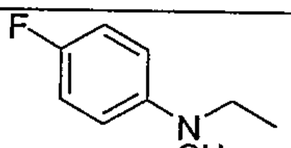
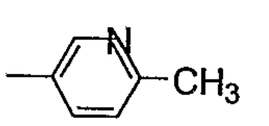
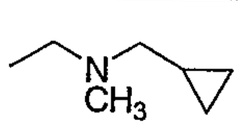
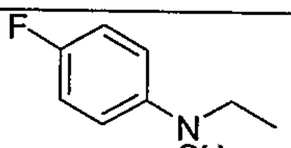
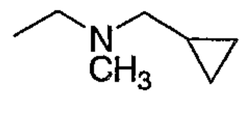
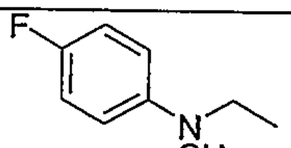
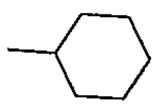
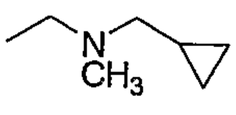
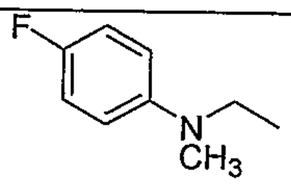
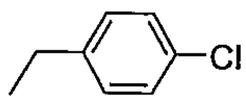
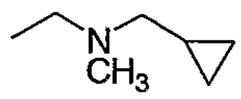
D491			
D492			
D493			
D494			
D495			
D496			
D497			
D498			
D499			
D500			
D501			
D502			
D503			
D504			

D505			
D506			
D507			
D508			
D509			
D510			
D511			
D512			
D513			
D514			
D515			
D516			
D517			

D518			
D519			
D520			
D521			
D522			
D523			
D524			
D525			
D526			
D527			
D528			
D529			
D530			

D531			
D532			
D533			
D534			
D535			
D536			
D537			
D538			
D539			
D540			
D541			
D542			
D543			

D544			
D545			
D546			
D547			
D548			
D549			
D550			
D551			
D552			
D553			
D554			
D555			
D556			
D557			

D558			
D559			
D560			
D561			
D562			
D563			
D564			
D565			
D566			
D567			
D568			
D569		CH_3	
D570			
D571			

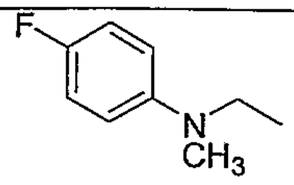
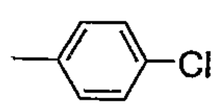
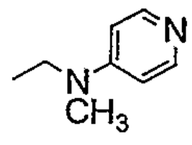
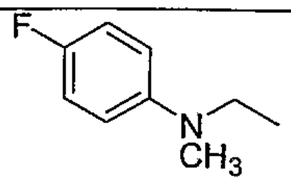
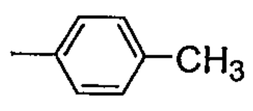
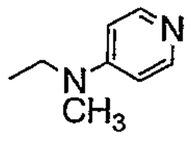
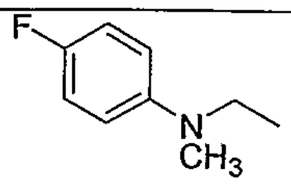
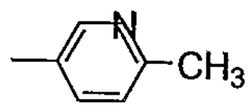
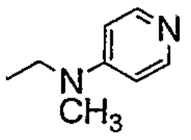
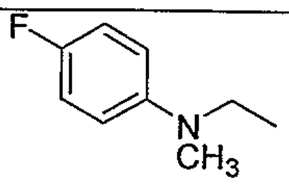
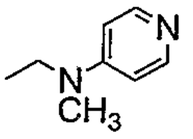
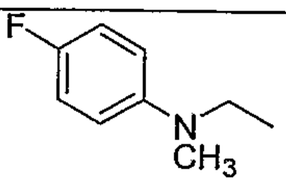
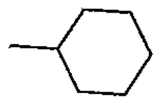
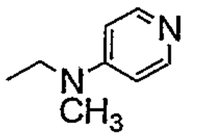
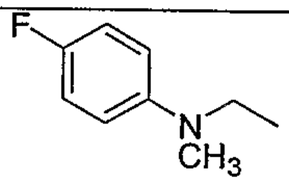
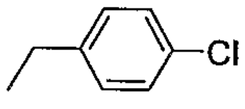
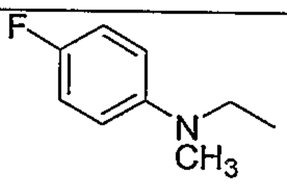
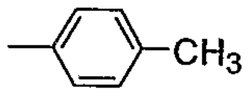
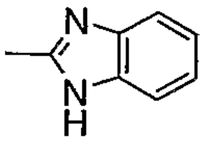
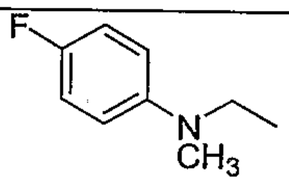
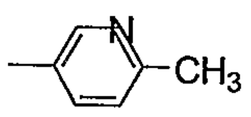
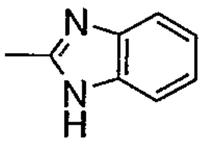
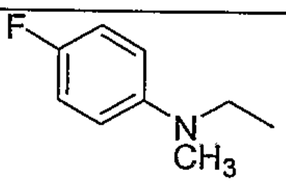
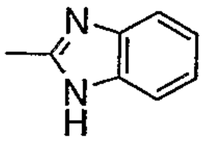
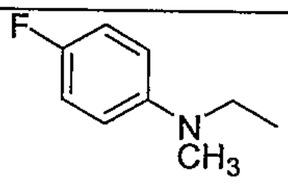
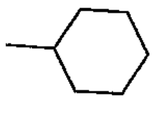
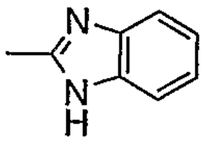
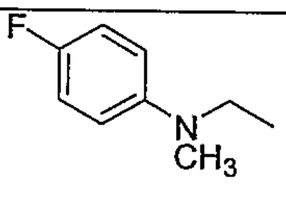
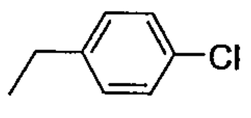
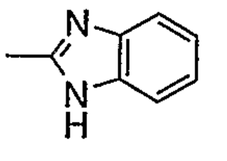
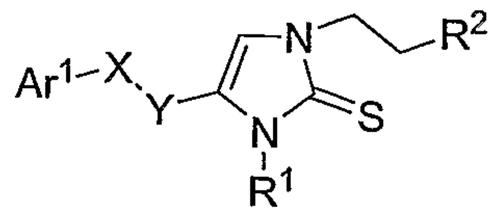
D572			
D573			
D574			
D575		CH_3	
D576			
D577			
D578			
D579			
D580		CH_3	
D581			
D582			

TABLE D-6



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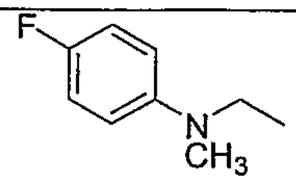
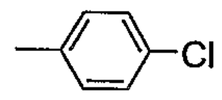
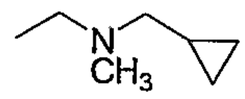
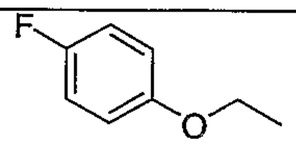
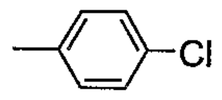
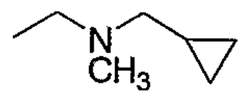
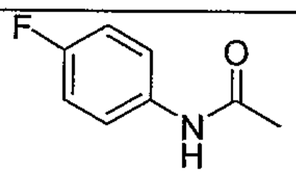
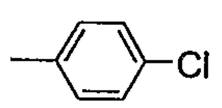
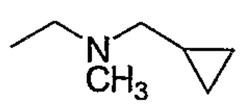
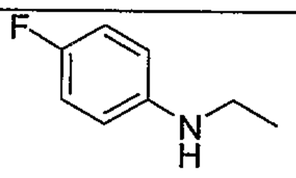
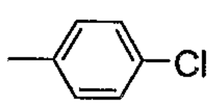
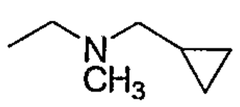
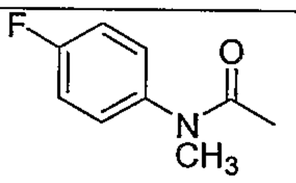
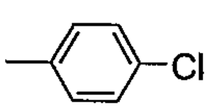
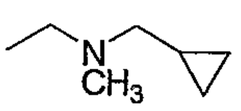
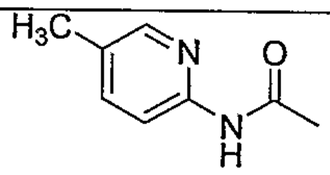
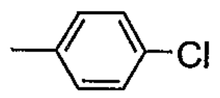
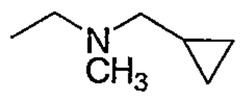
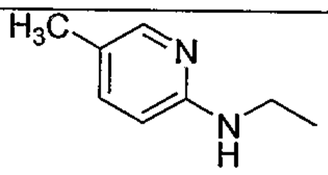
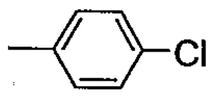
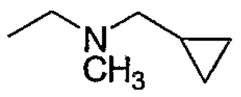
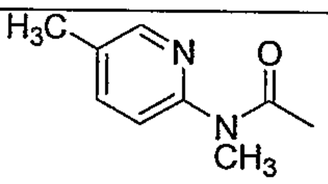
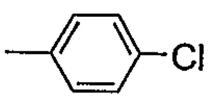
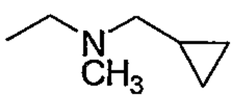
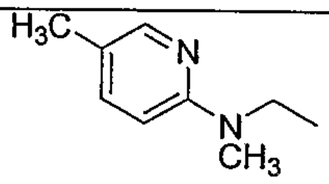
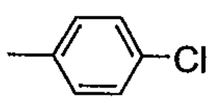
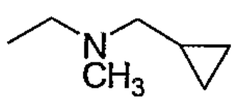
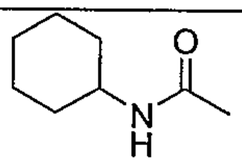
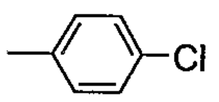
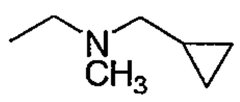
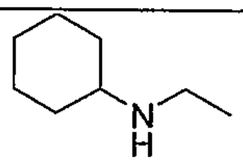
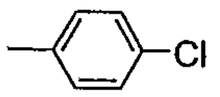
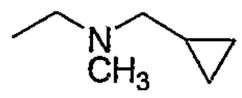
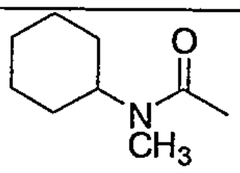
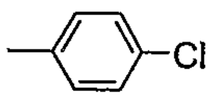
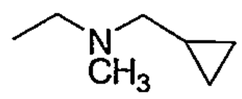
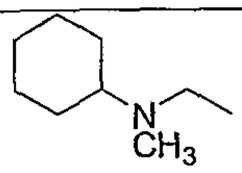
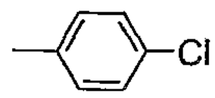
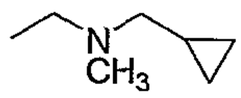
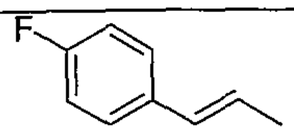
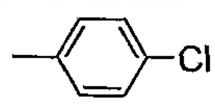
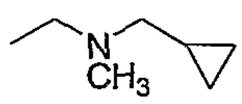
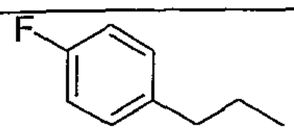
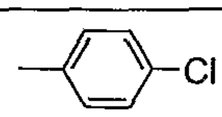
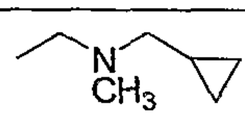
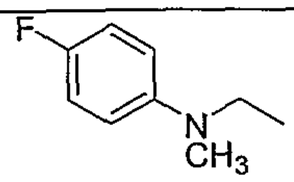
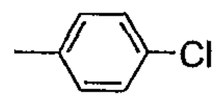
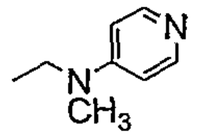
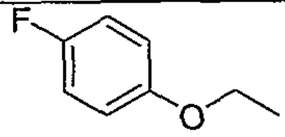
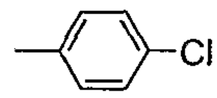
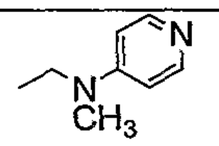
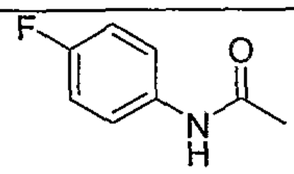
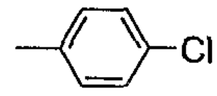
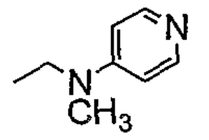
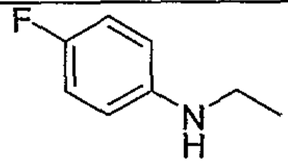
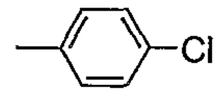
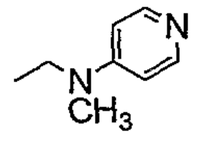
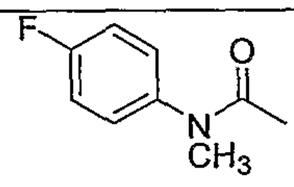
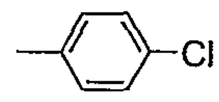
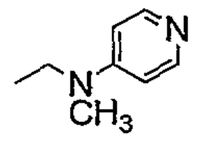
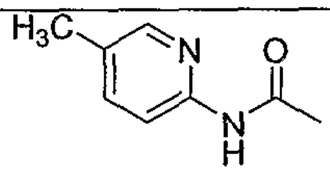
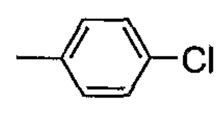
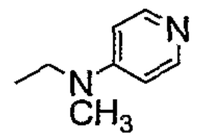
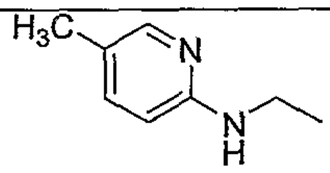
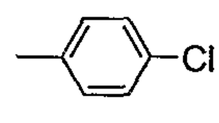
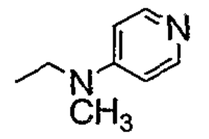
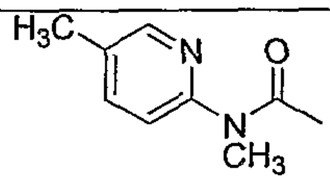
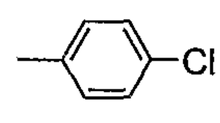
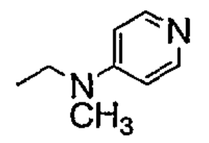
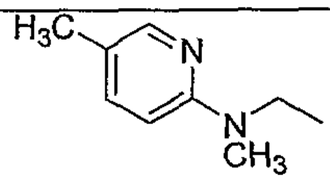
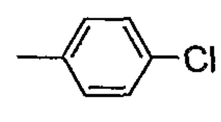
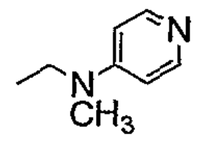
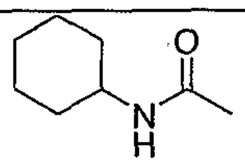
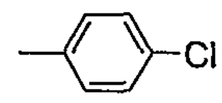
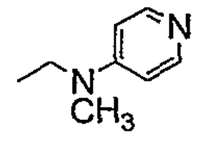
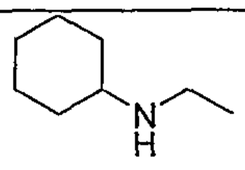
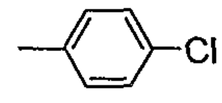
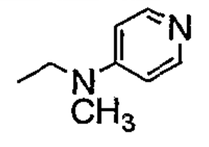
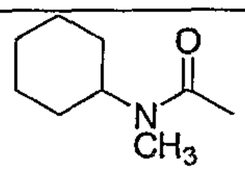
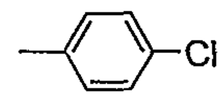
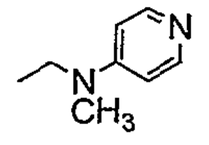
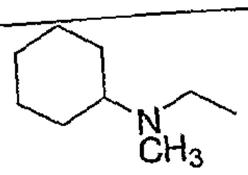
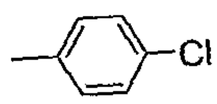
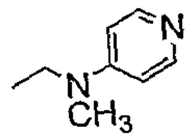
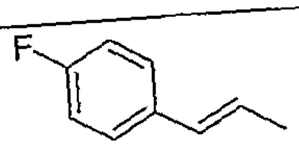
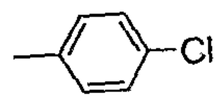
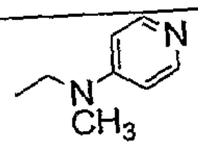
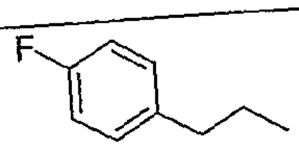
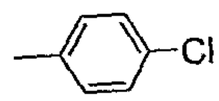
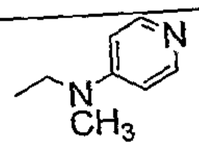
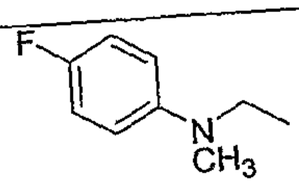
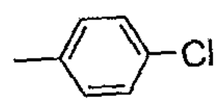
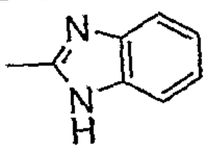
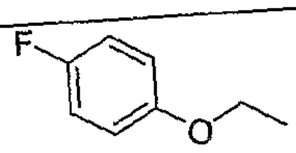
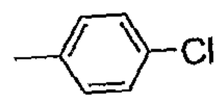
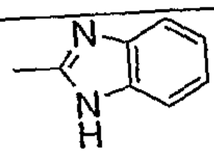
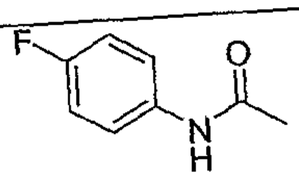
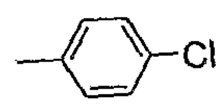
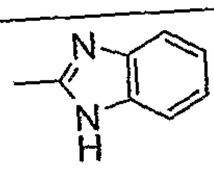
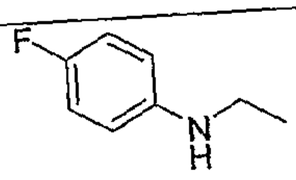
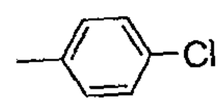
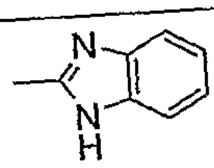
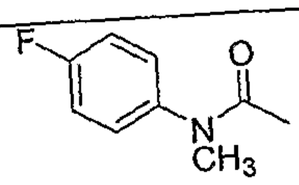
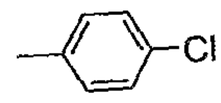
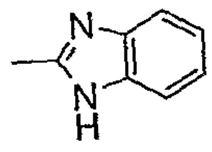
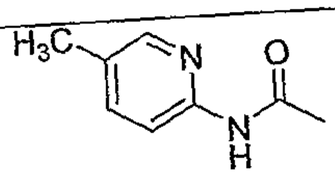
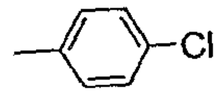
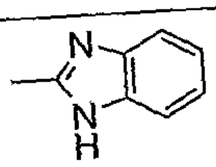
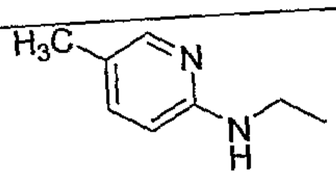
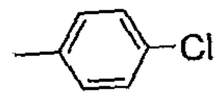
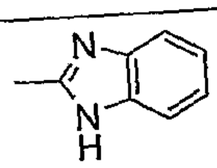
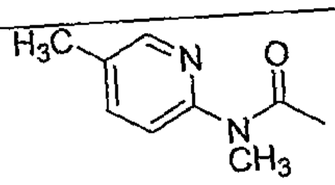
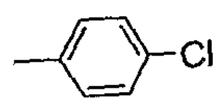
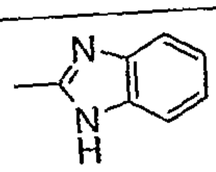
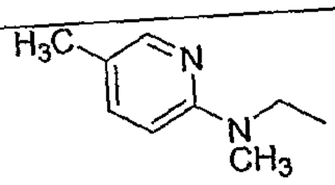
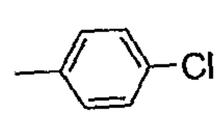
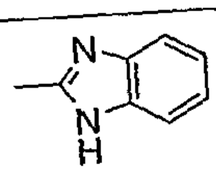
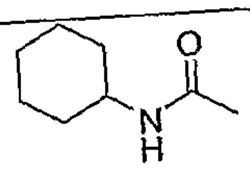
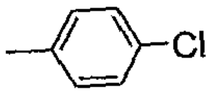
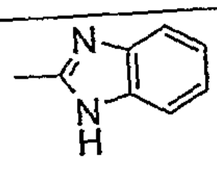
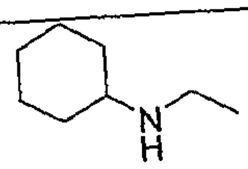
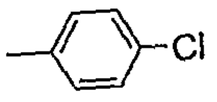
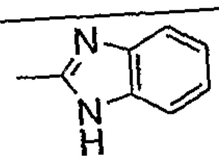
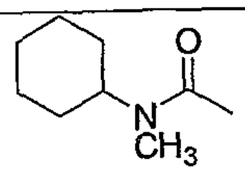
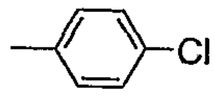
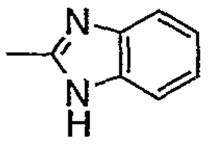
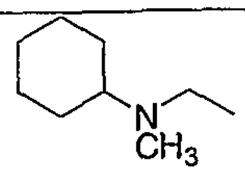
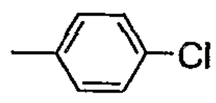
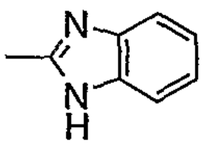
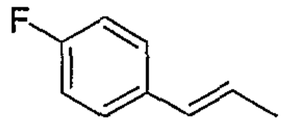
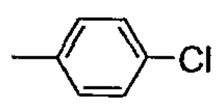
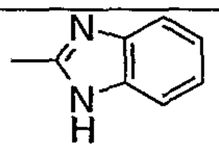
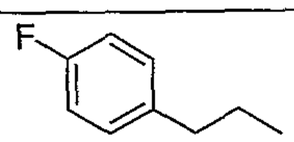
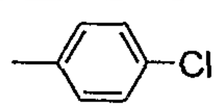
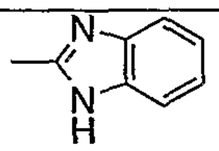
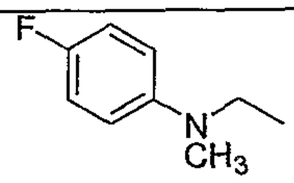
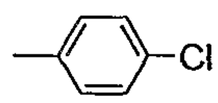
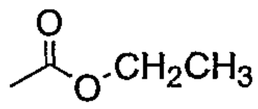
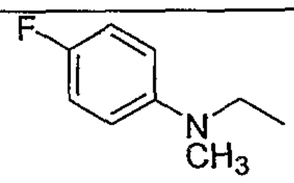
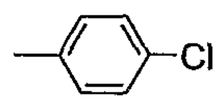
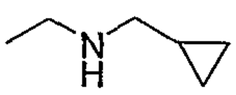
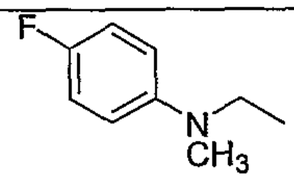
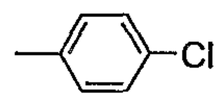
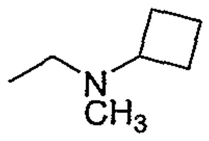
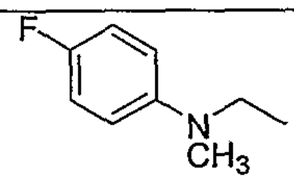
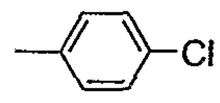
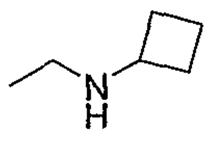
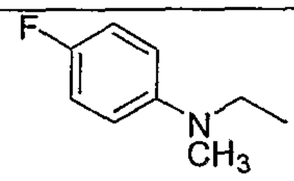
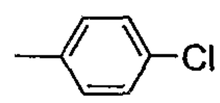
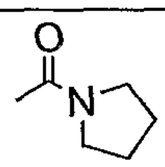
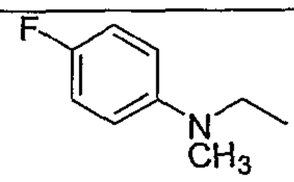
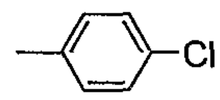
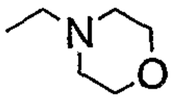
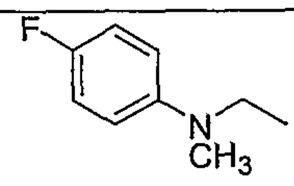
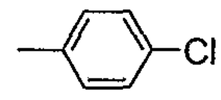
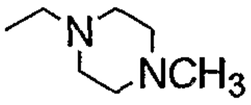
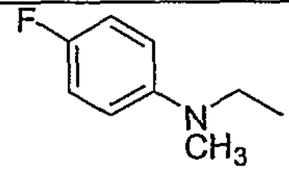
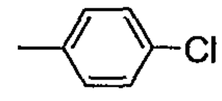
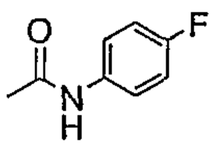
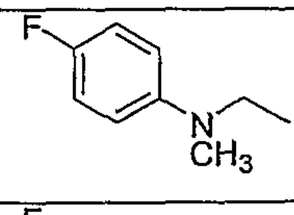
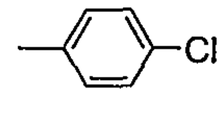
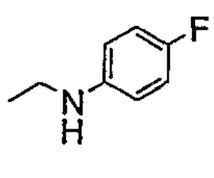
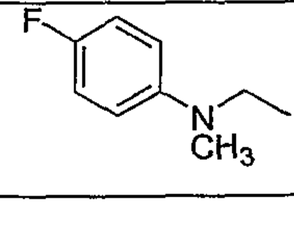
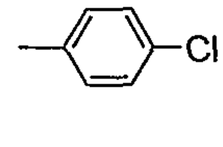
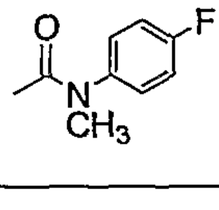
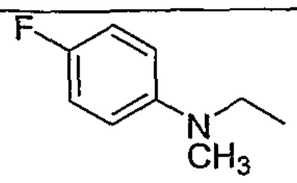
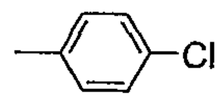
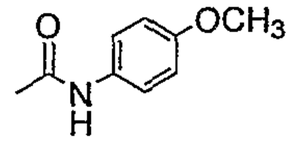
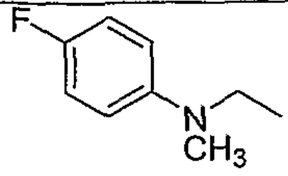
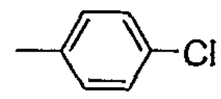
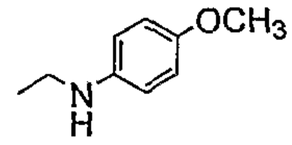
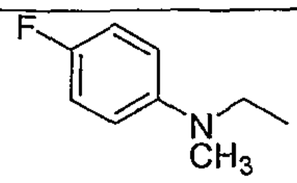
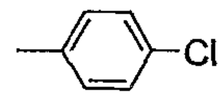
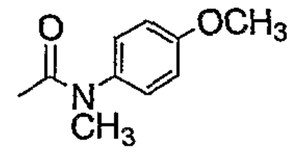
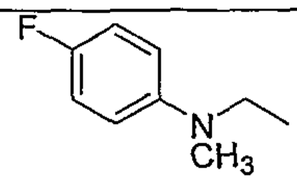
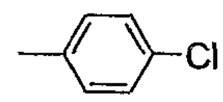
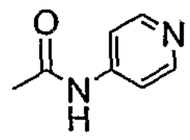
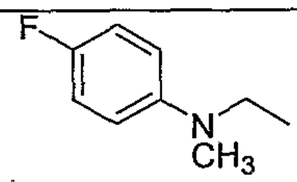
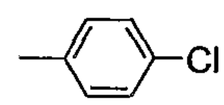
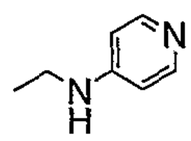
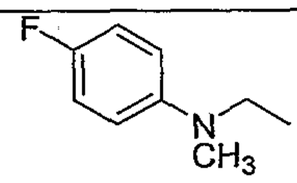
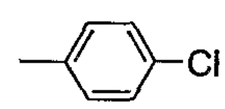
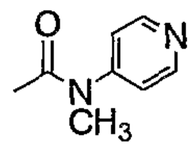
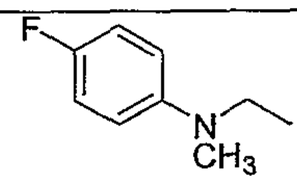
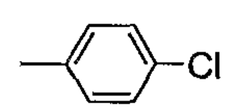
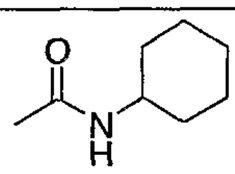
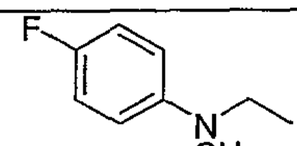
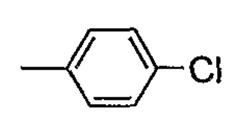
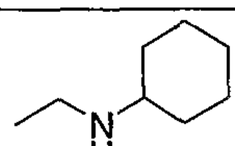
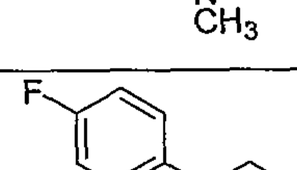
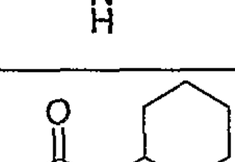
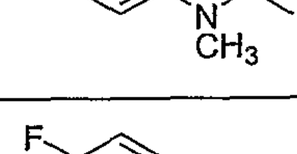
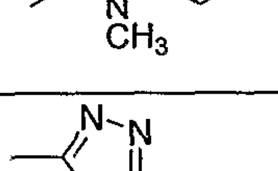
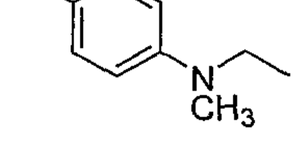
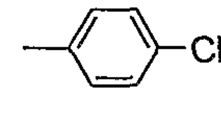
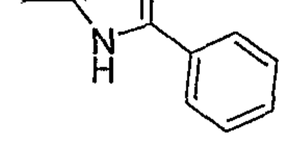
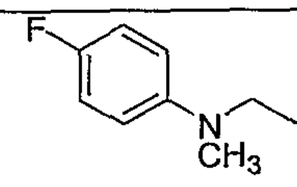
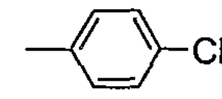
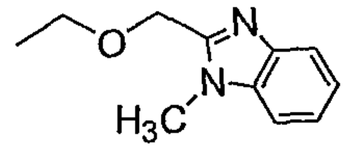
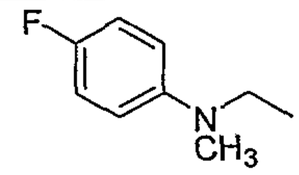
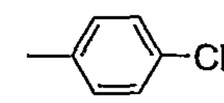
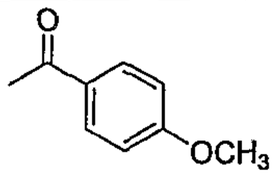
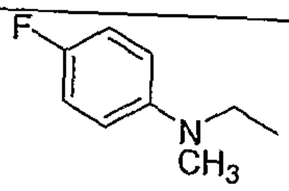
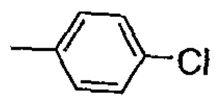
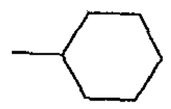
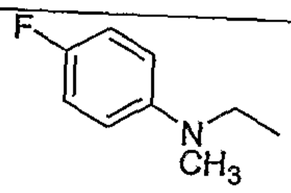
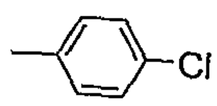
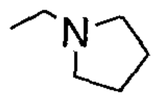
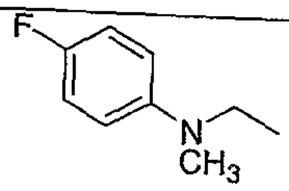
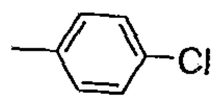
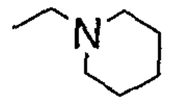
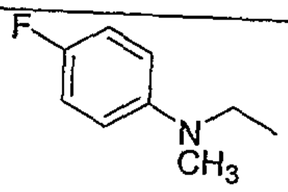
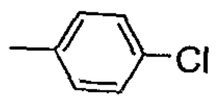
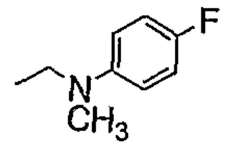
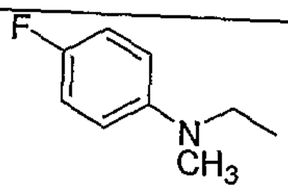
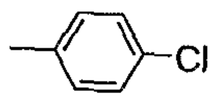
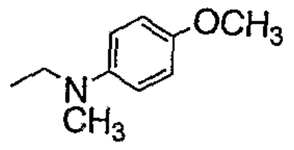
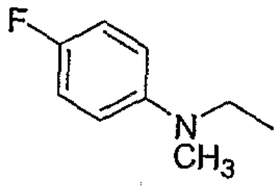
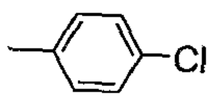
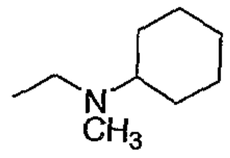
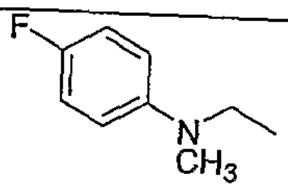
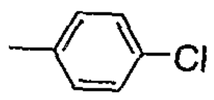
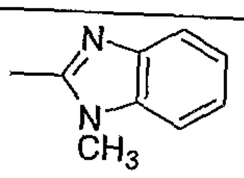
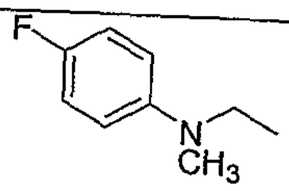
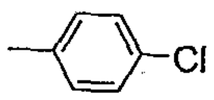
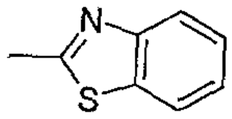
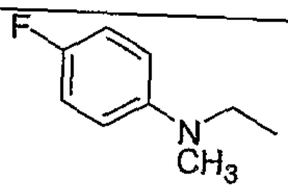
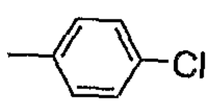
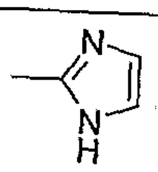
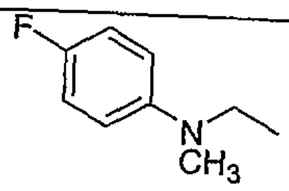
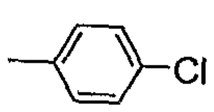
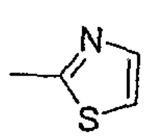
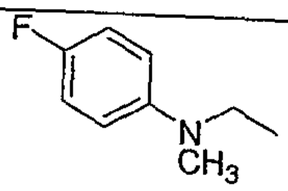
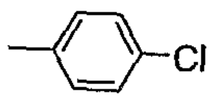
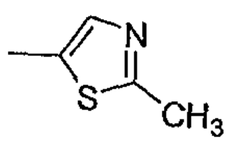
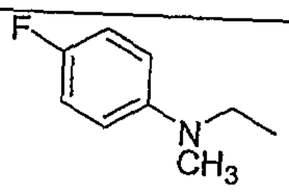
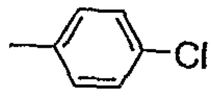
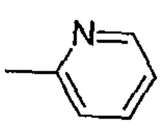
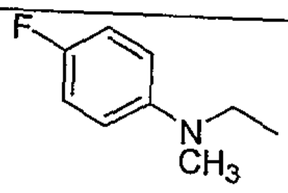
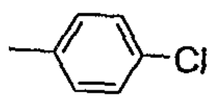
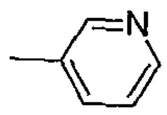
D583			
D584			
D585			
D586			
D587			
D588			
D589			
D590			
D591			
D592			
D593			
D594			

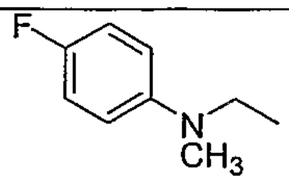
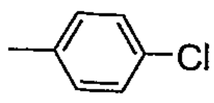
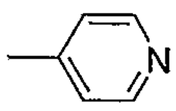
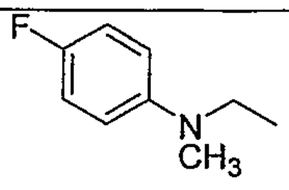
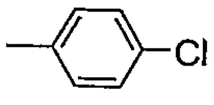
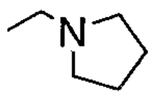
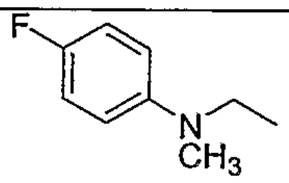
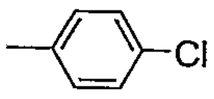
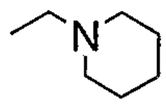
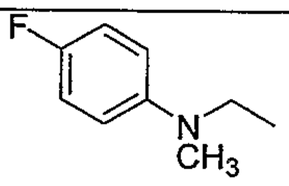
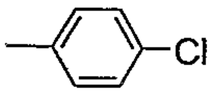
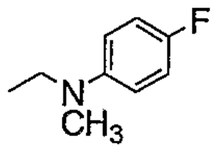
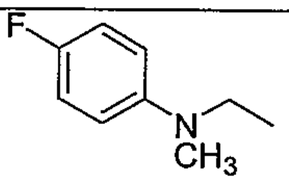
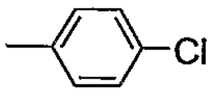
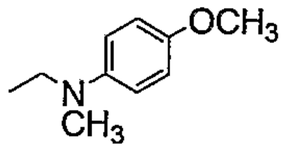
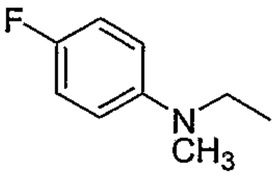
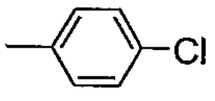
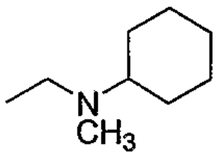
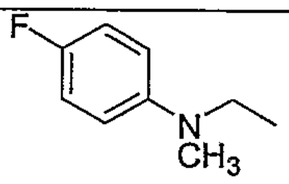
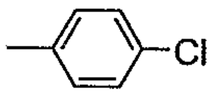
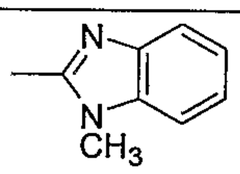
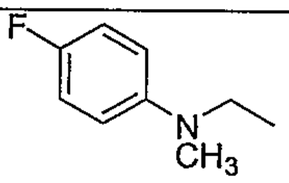
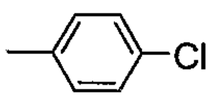
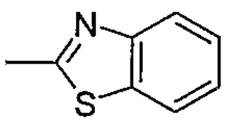
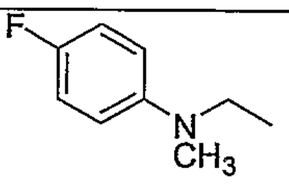
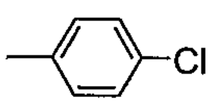
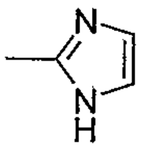
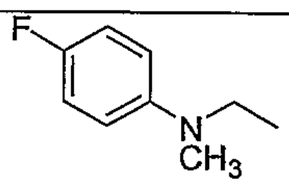
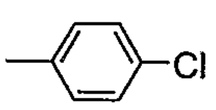
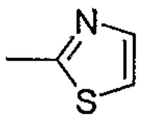
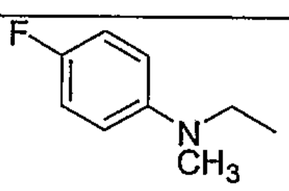
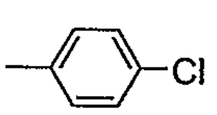
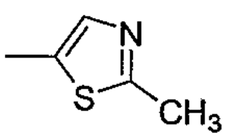
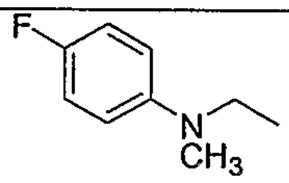
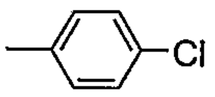
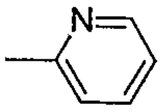
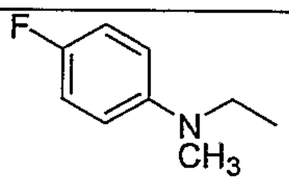
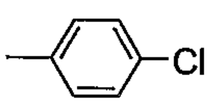
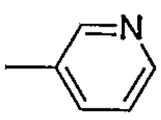
D595			
D596			
D597			
D598			
D599			
D600			
D601			
D602			
D603			
D604			
D605			
D606			
D607			
D608			
D609			

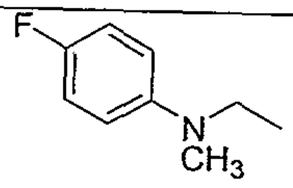
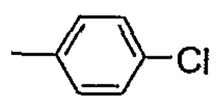
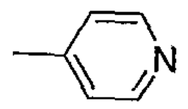
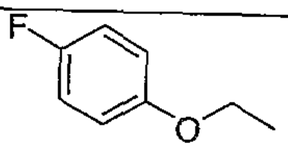
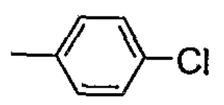
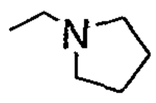
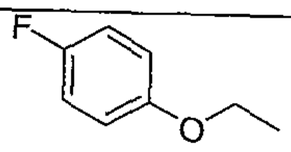
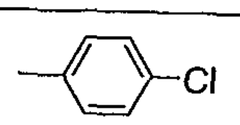
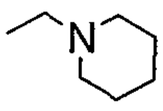
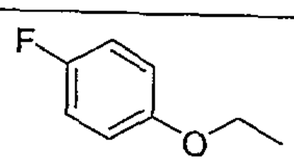
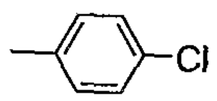
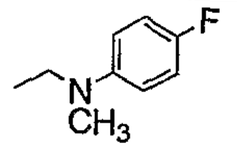
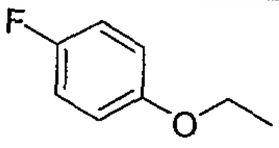
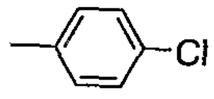
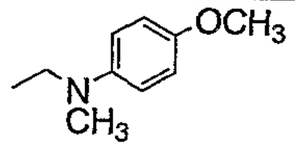
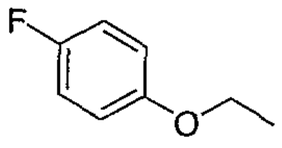
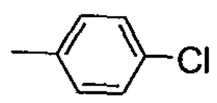
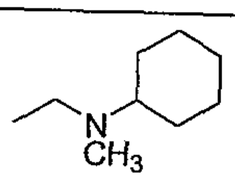
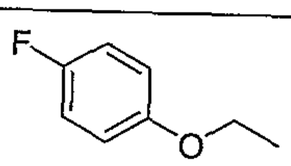
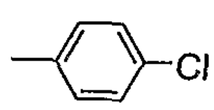
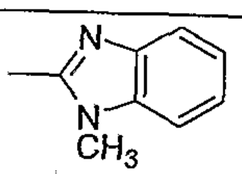
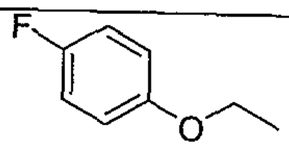
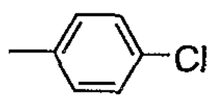
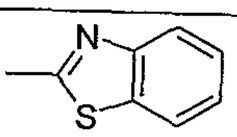
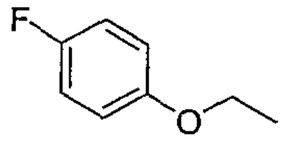
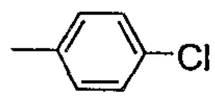
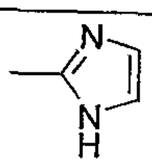
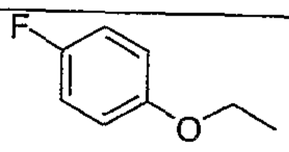
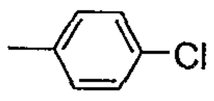
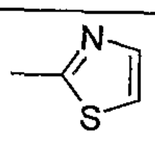
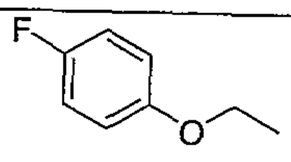
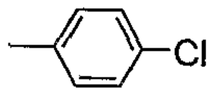
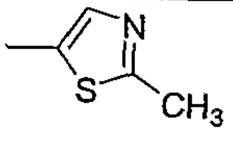
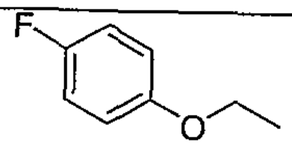
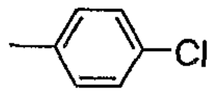
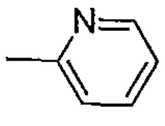
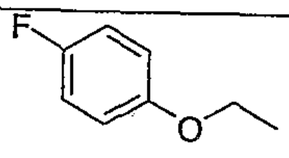
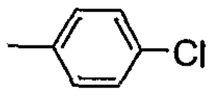
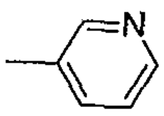
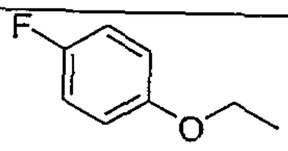
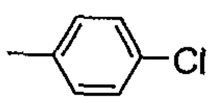
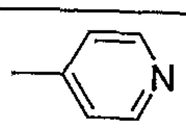
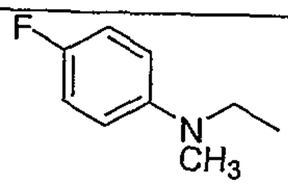
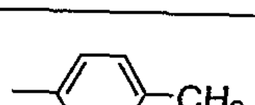
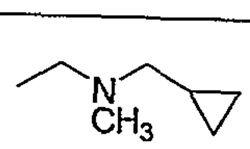
D610			
D611			
D612			
D613			
D614			
D615			
D616			
D617			
D618			
D619			
D620			
D621			
D622			
D623			

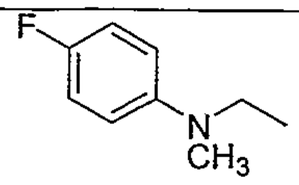
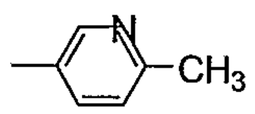
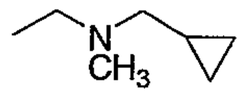
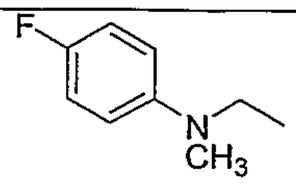
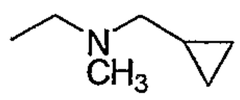
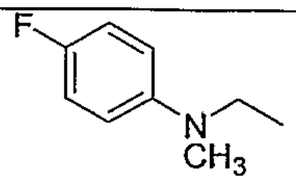
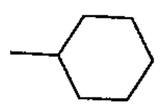
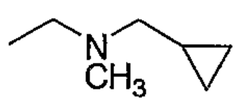
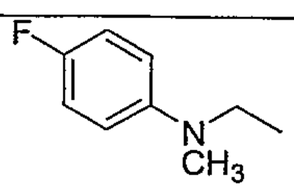
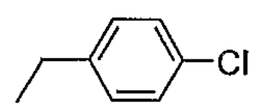
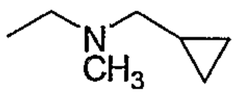
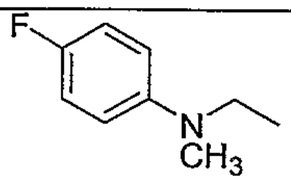
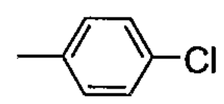
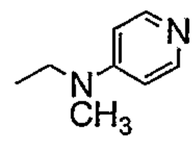
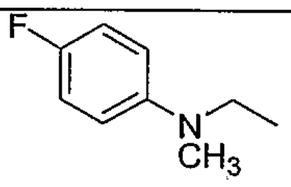
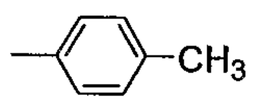
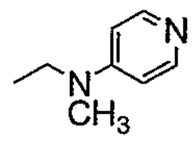
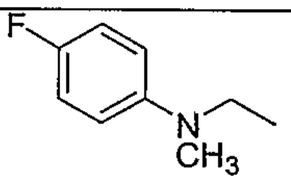
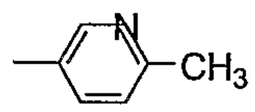
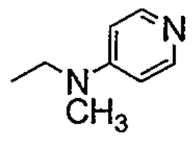
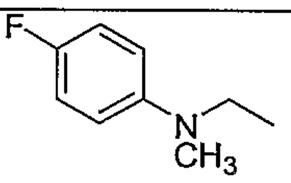
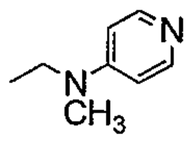
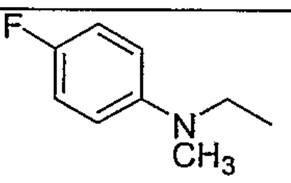
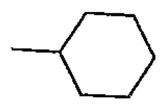
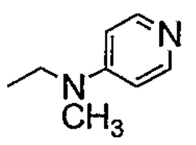
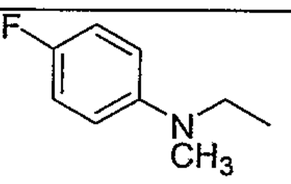
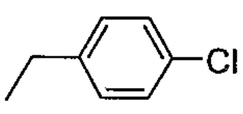
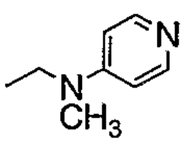
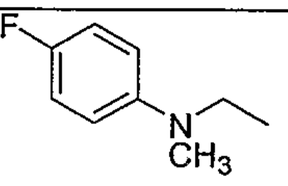
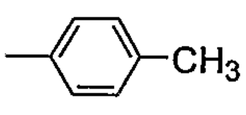
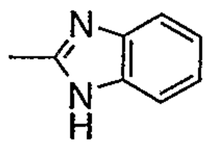
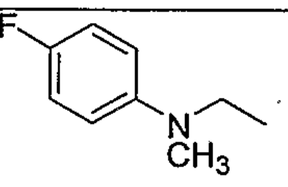
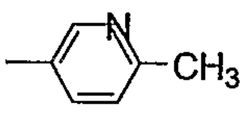
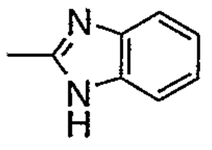
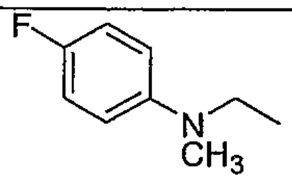
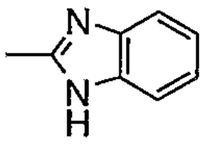
D624			
D625			
D626			
D627			
D628			
D629			
D630			
D631			
D632			
D633			
D634			
D635			
D636			
D637			

D638			
D639			
D640			
D641			
D642			
D643			
D644			
D645			
D646			
D647			
D648			
D649			
D650			

D651			
D652			
D653			
D654			
D655			
D656			
D657			
D658			
D659			
D660			
D661			
D662			
D663			

D664			
D665			
D666			
D667			
D668			
D669			
D670			
D671			
D672			
D673			
D674			
D675			
D676			

D677			
D678			
D679			
D680			
D681			
D682			
D683			
D684			
D685			
D686			
D687			
D688			
D689			
D690			
D691			

D692			
D693		CH_3	
D694			
D695			
D696			
D697			
D698			
D699		CH_3	
D700			
D701			
D702			
D703			
D704		CH_3	

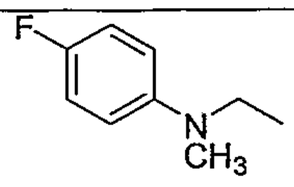
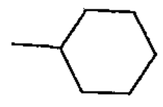
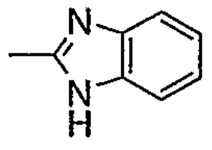
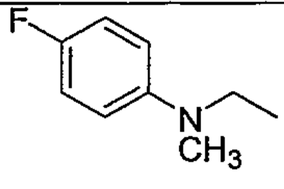
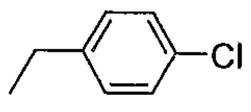
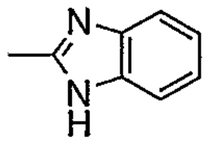
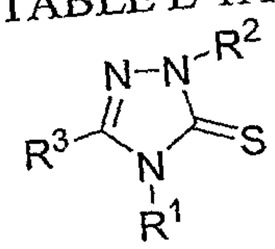
D705			
D706			

TABLE E-1A



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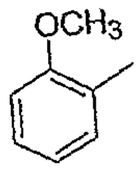
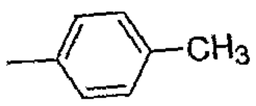
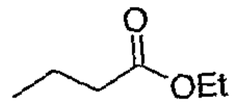
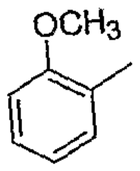
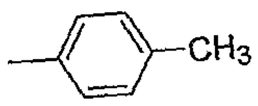
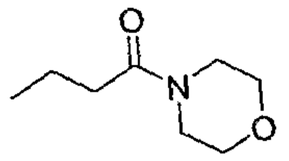
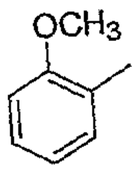
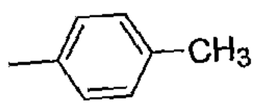
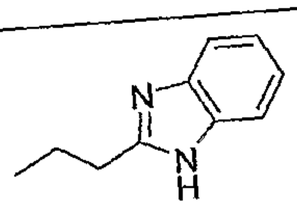
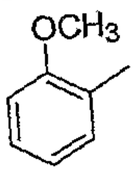
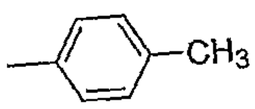
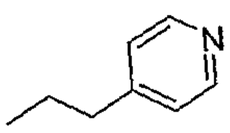
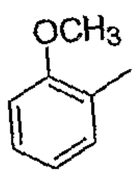
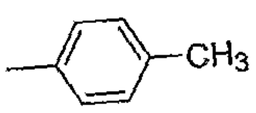
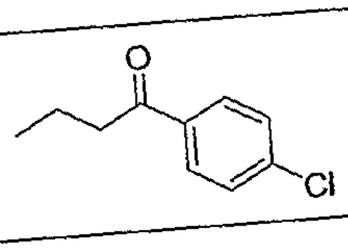
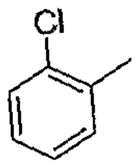
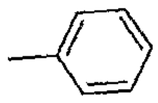
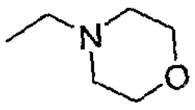
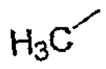
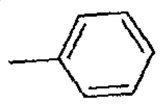
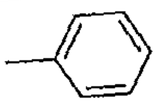
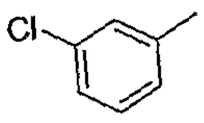
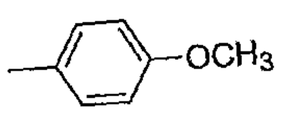
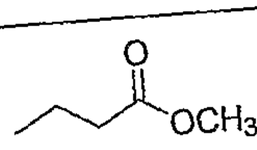
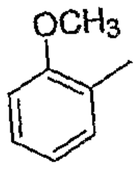
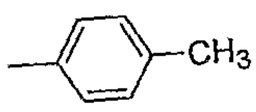
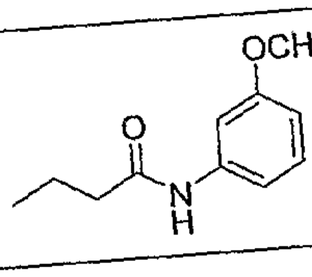
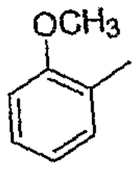
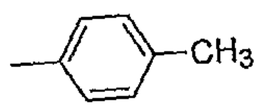
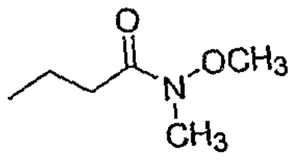
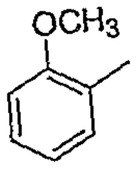
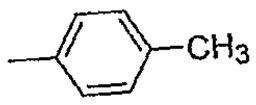
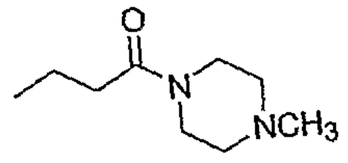
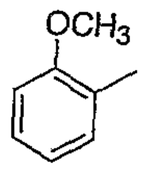
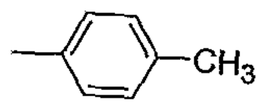
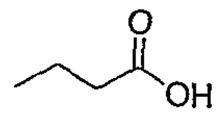
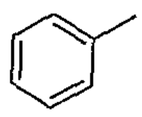
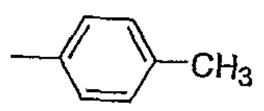
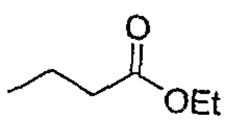
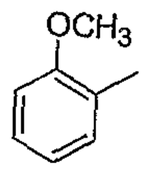
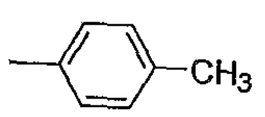
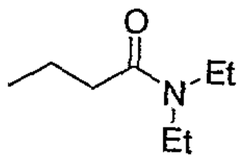
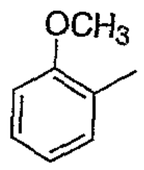
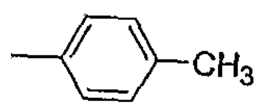
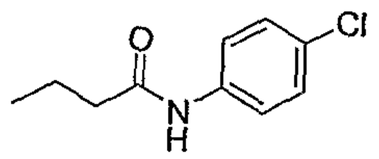
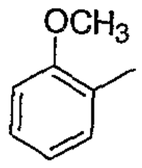
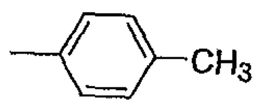
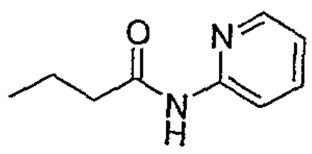
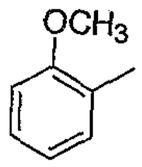
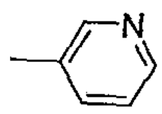
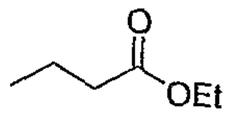
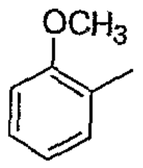
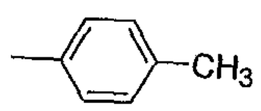
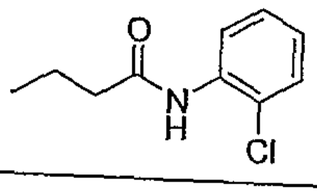
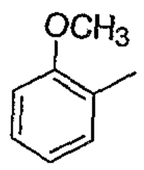
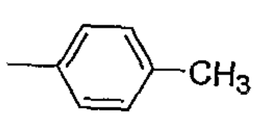
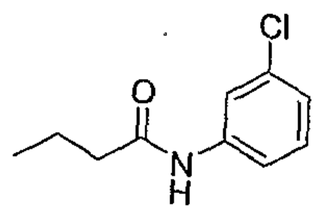
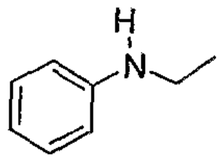
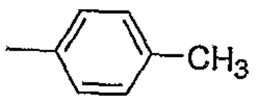
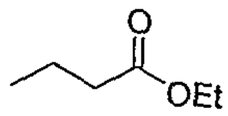
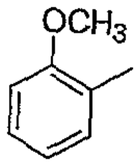
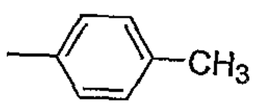
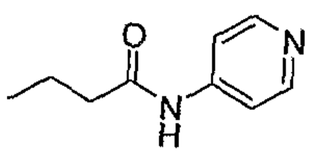
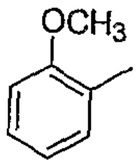
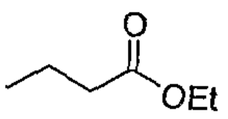
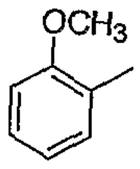
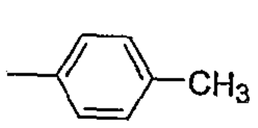
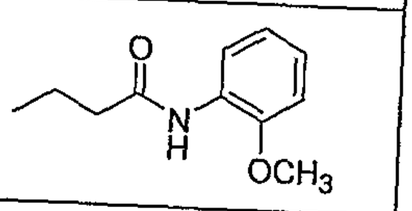
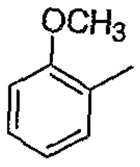
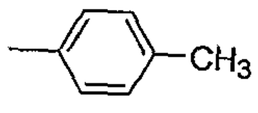
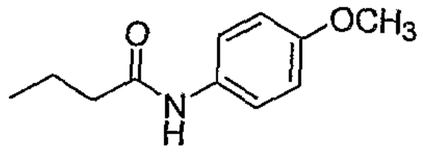
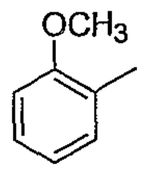
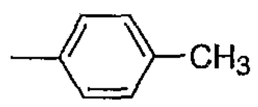
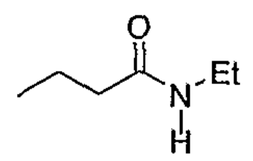
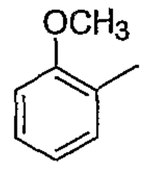
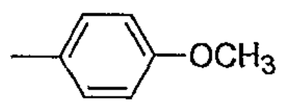
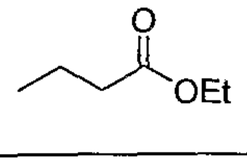
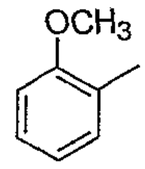
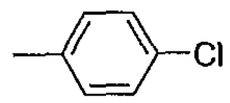
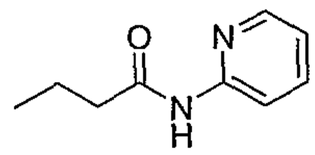
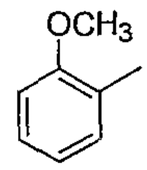
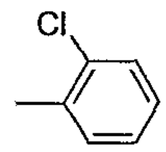
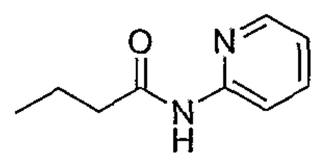
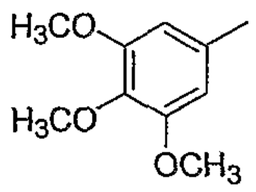
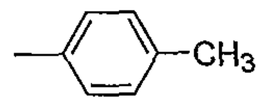
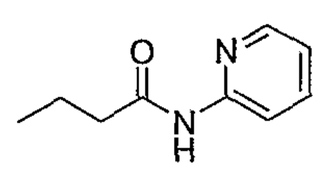
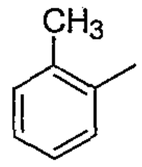
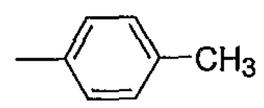
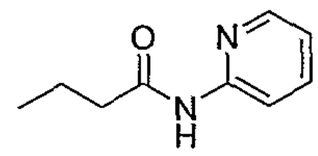
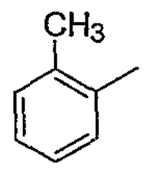
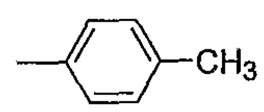
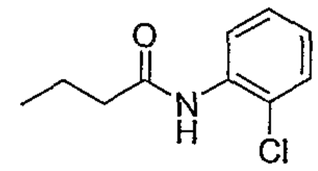
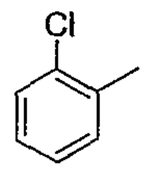
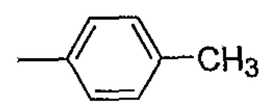
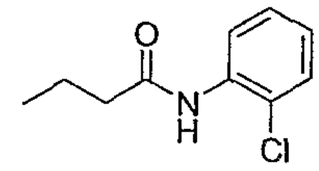
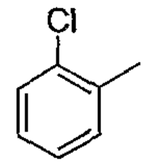
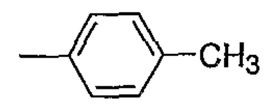
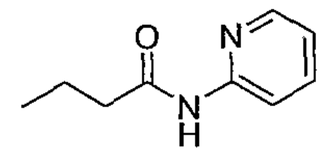
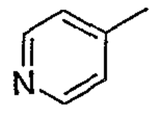
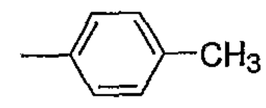
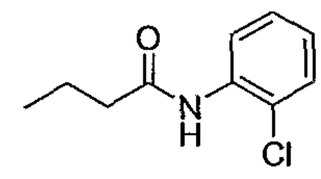
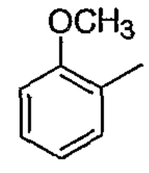
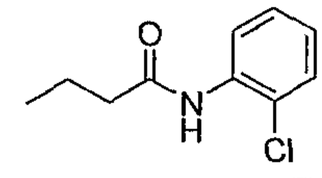
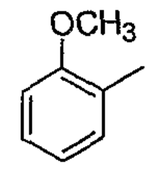
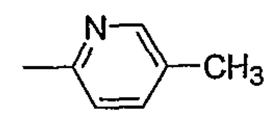
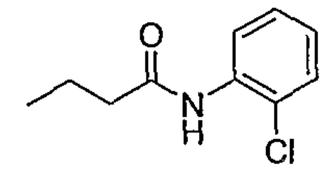
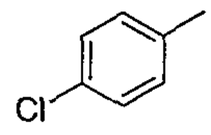
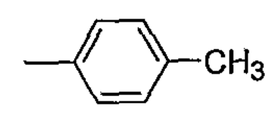
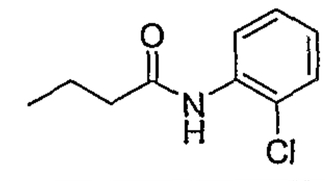
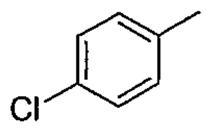
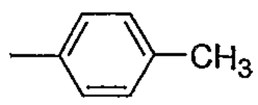
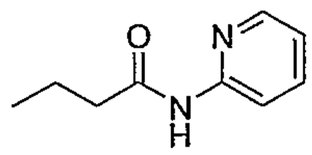
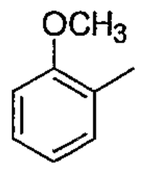
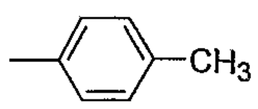
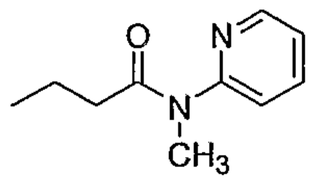
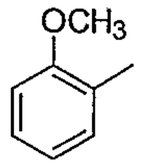
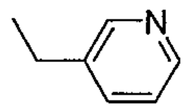
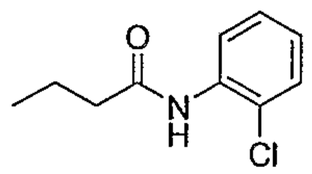
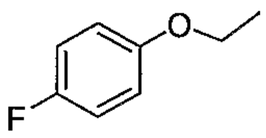
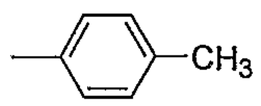
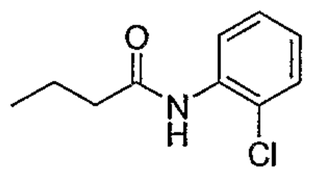
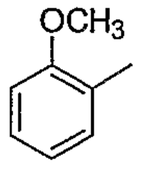
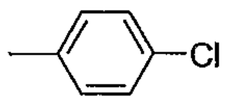
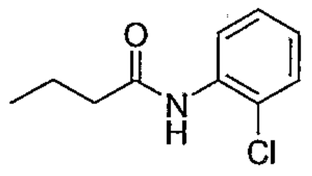
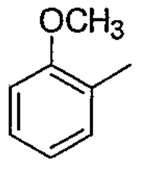
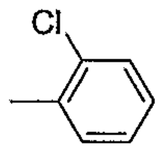
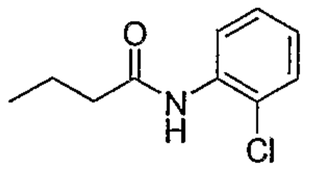
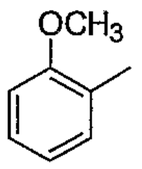
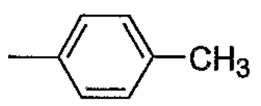
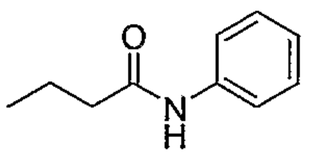
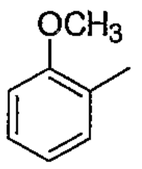
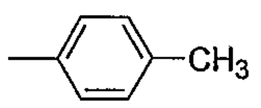
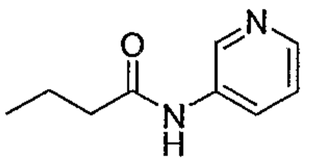
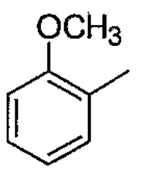
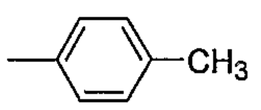
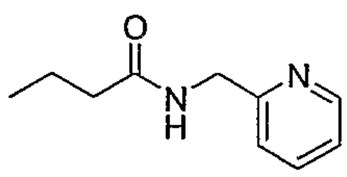
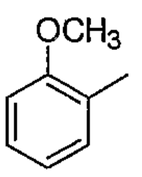
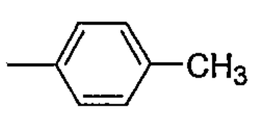
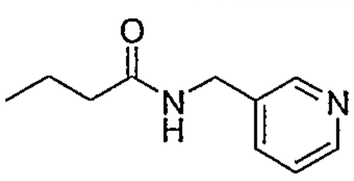
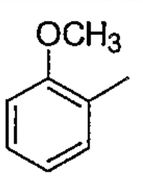
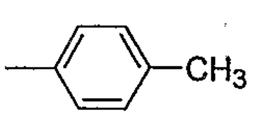
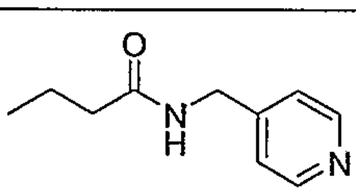
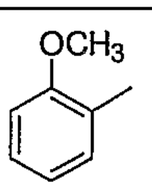
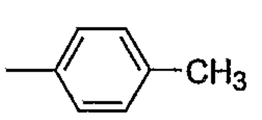
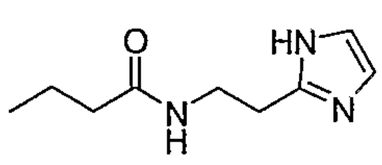
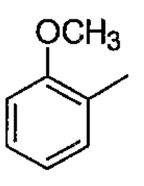
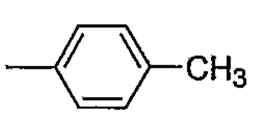
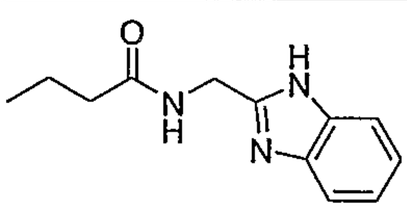
E1			
E2			
E3			
E4			
E5			
E6			
E7			
E8			
E9			
E10			
E11			

E12			
E13			
E14			
E15			
E16			
E17			
E18			
E19			
E20			
E21			
E22		CH3	
E23			
E24			

E25			
E26			
E27			
E28			
E29			
E30			
E31			
E32			
E33			
E34			
E35		i-Pr	
E36			
E37			

E38			
E39			
E40			
E41			
E42			
E43			
E44			
E45			
E46			
E47			
E48			
E49			
E50			

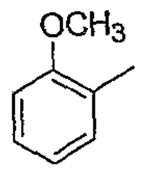
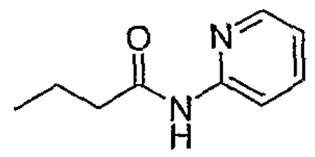
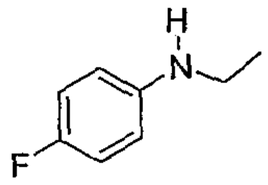
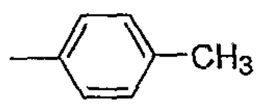
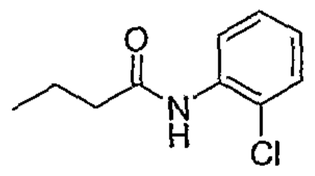
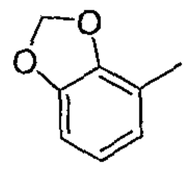
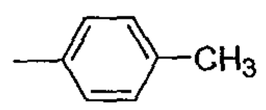
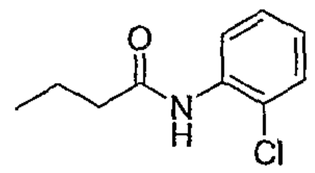
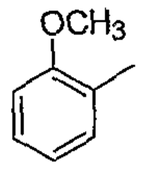
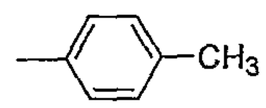
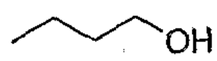
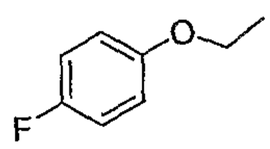
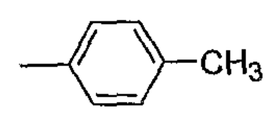
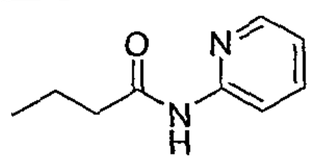
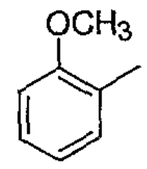
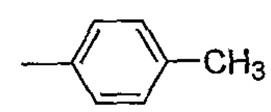
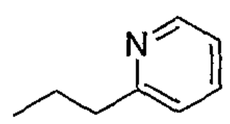
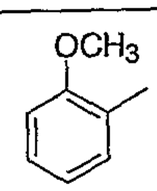
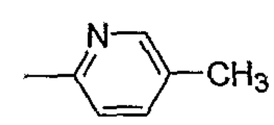
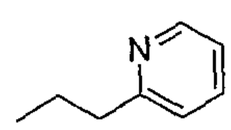
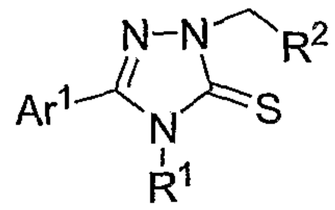
E51		i-Pr	
E52			
E53			
E54			
E55			
E56			
E57			

TABLE E-1B



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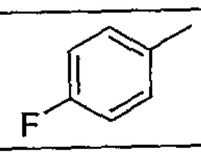
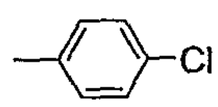
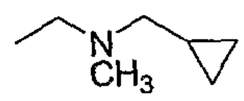
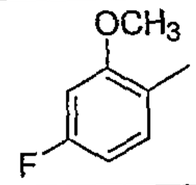
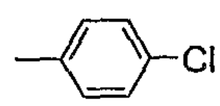
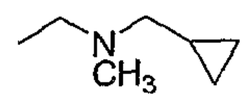
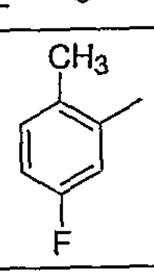
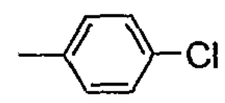
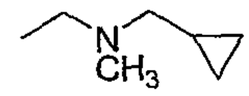
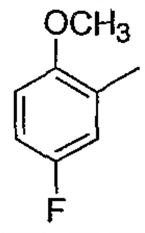
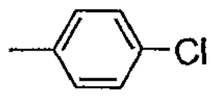
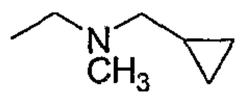
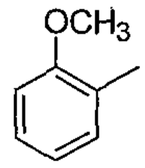
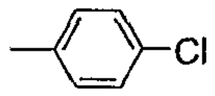
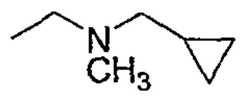
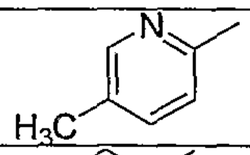
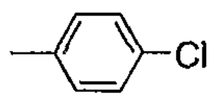
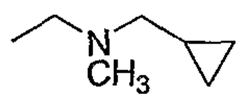
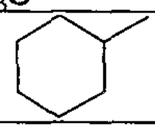
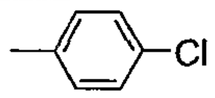
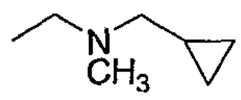
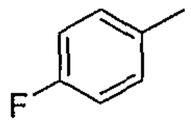
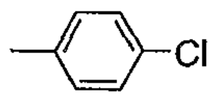
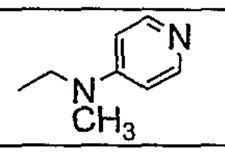
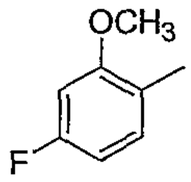
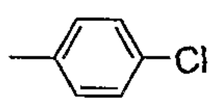
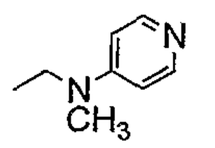
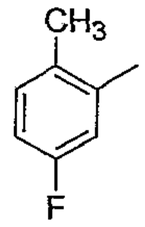
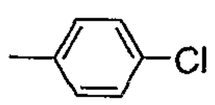
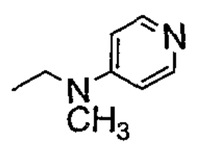
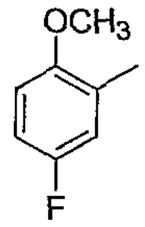
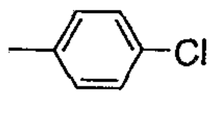
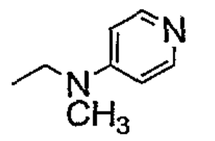
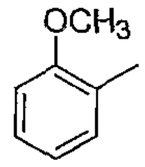
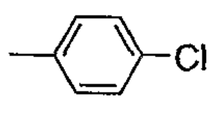
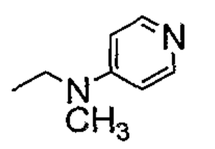
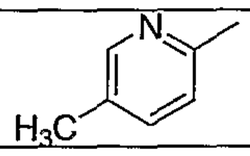
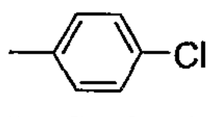
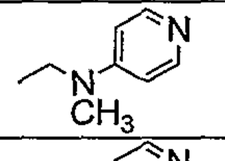
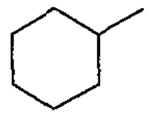
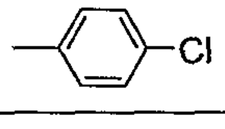
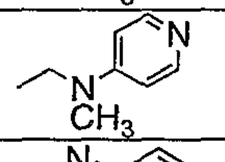
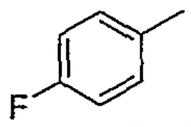
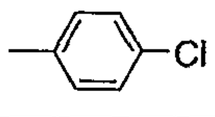
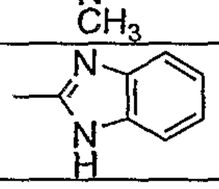
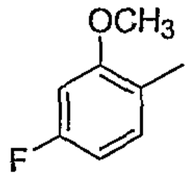
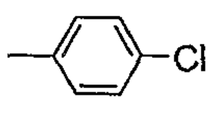
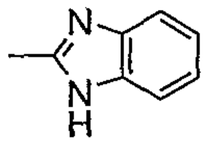
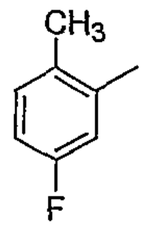
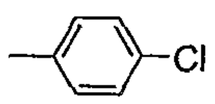
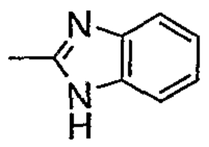
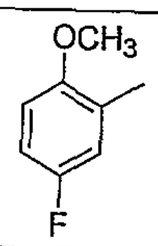
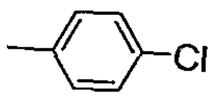
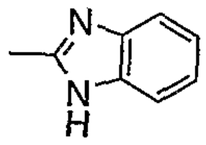
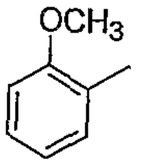
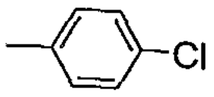
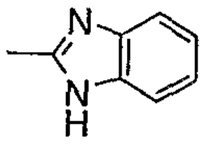
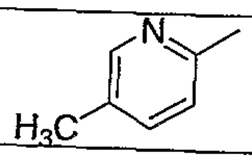
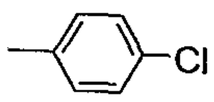
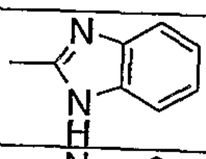
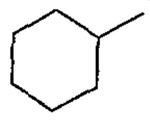
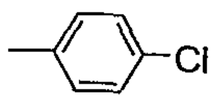
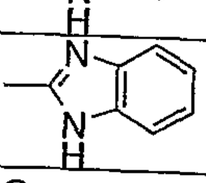
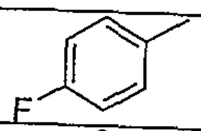
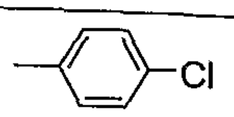
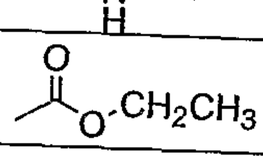
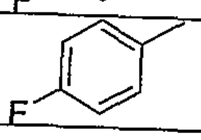
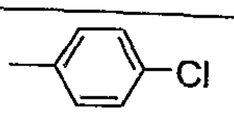
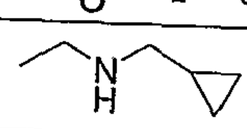
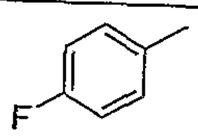
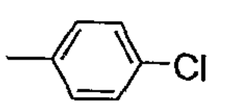
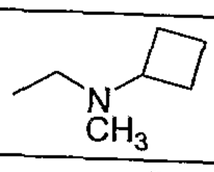
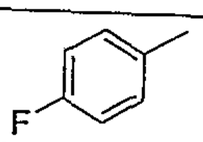
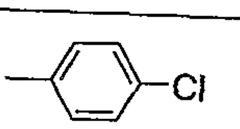
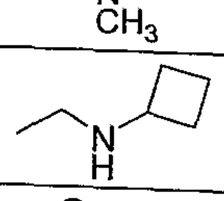
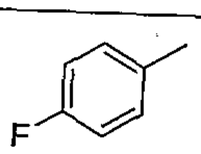
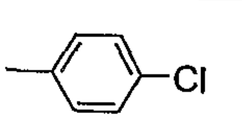
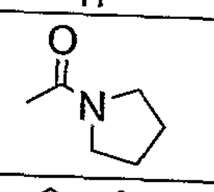
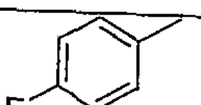
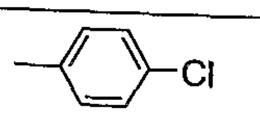
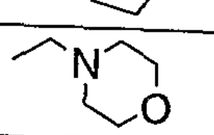
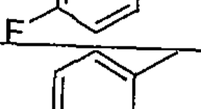
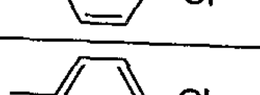
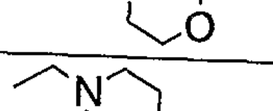
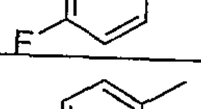
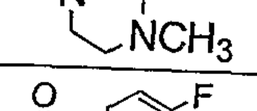
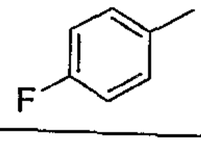
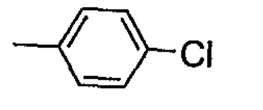
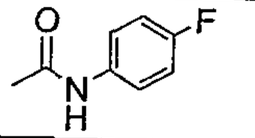
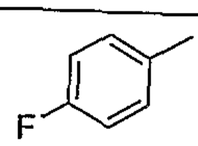
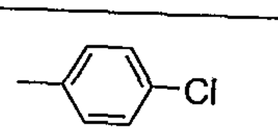
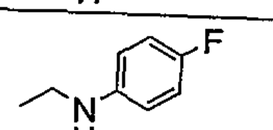
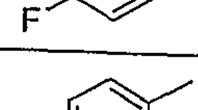
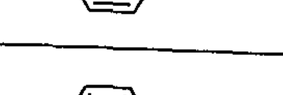
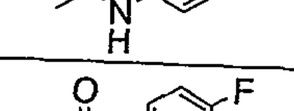
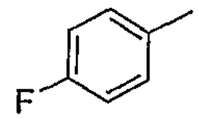
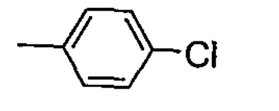
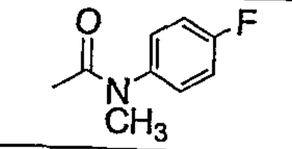
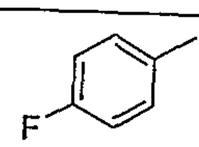
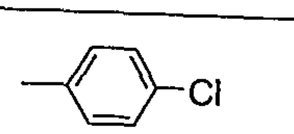
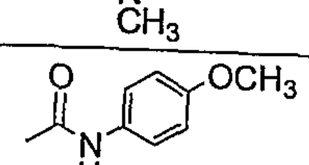
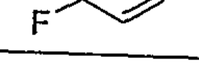
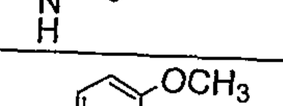
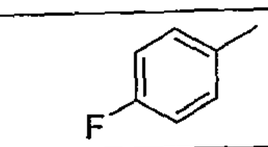
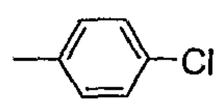
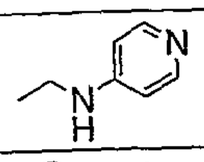
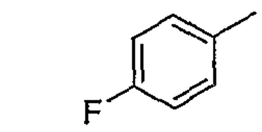
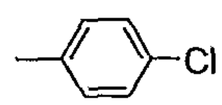
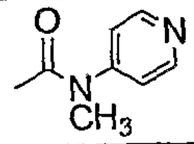
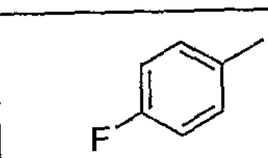
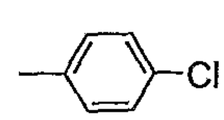
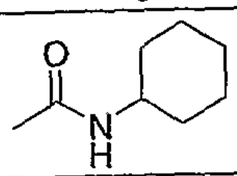
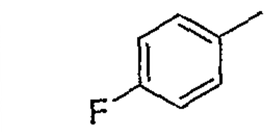
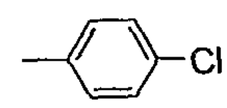
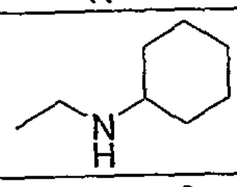
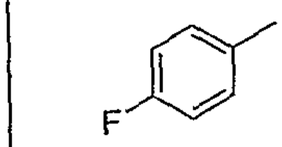
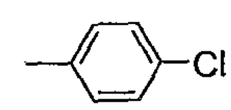
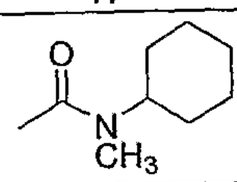
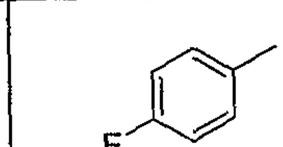
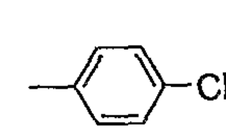
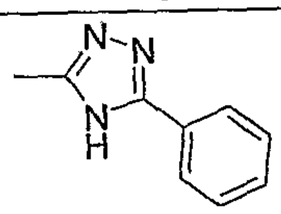
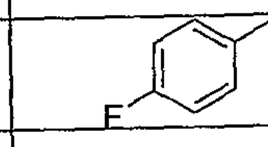
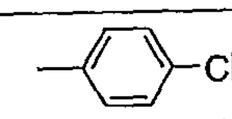
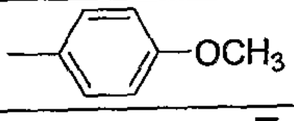
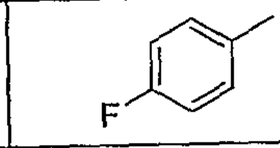
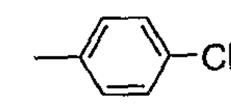
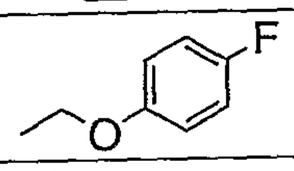
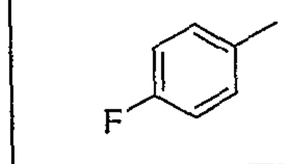
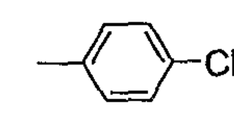
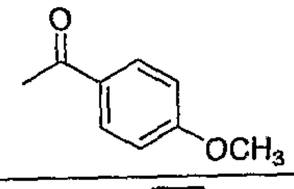
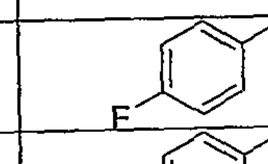
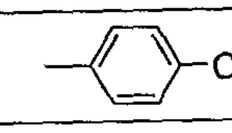
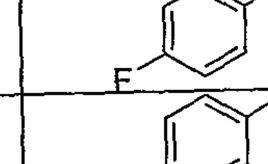
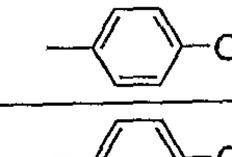
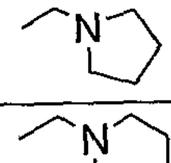
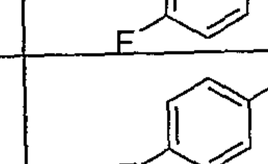
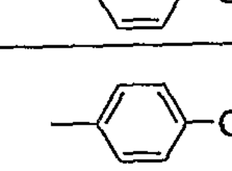
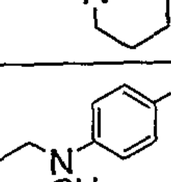
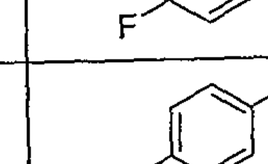
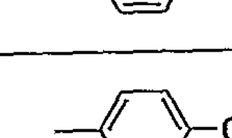
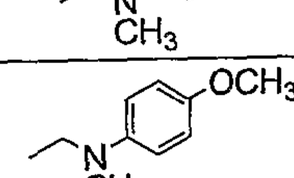
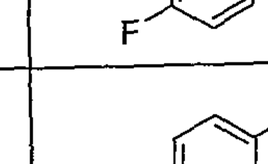
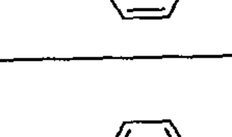
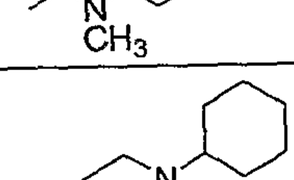
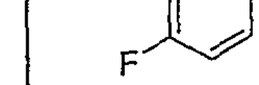
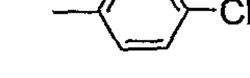
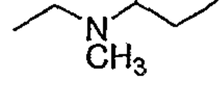
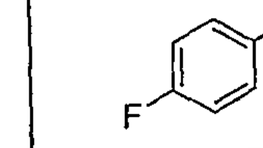
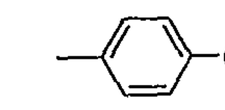
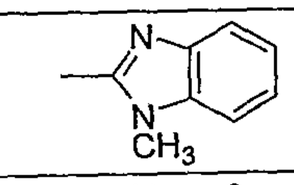
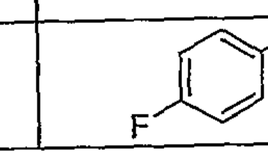
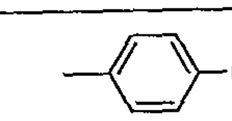
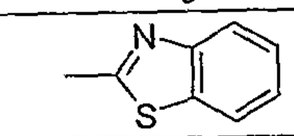
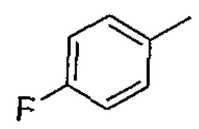
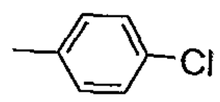
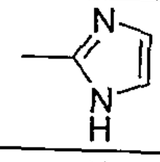
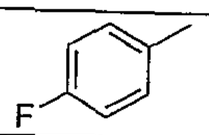
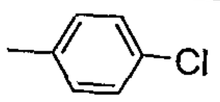
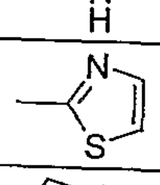
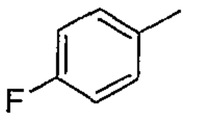
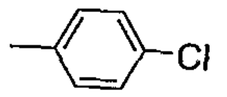
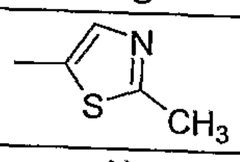
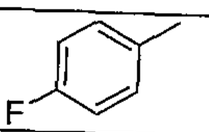
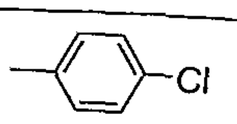
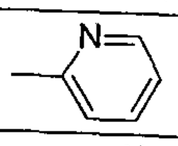
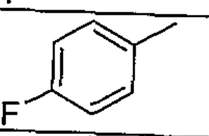
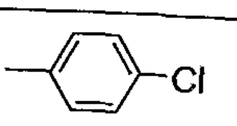
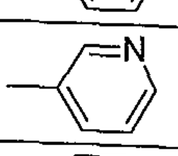
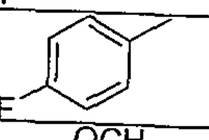
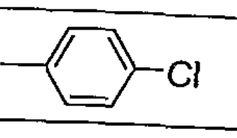
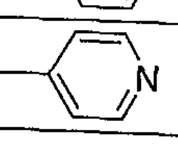
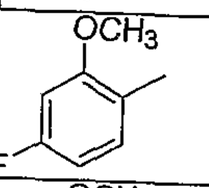
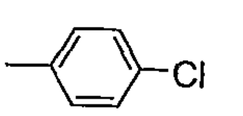
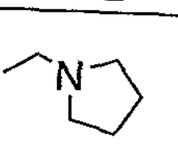
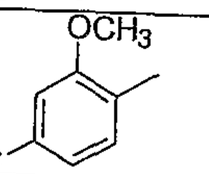
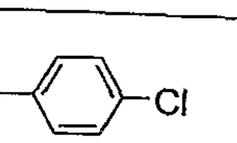
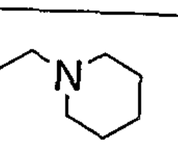
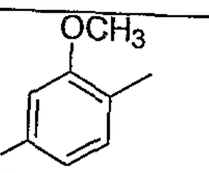
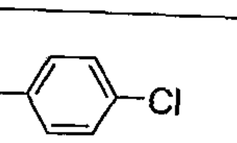
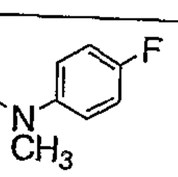
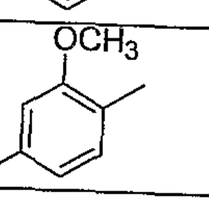
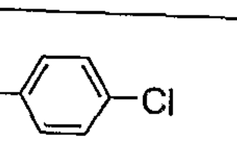
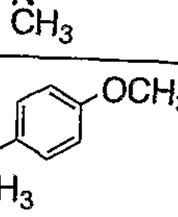
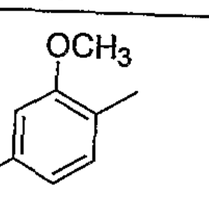
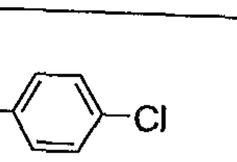
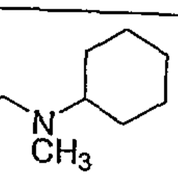
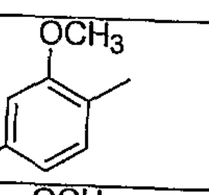
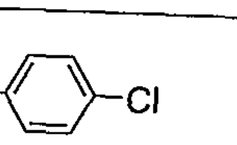
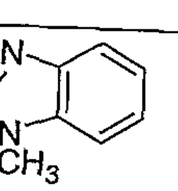
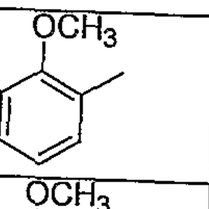
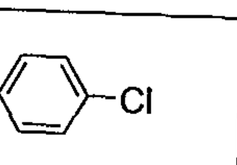
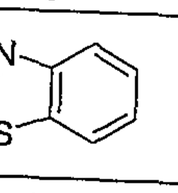
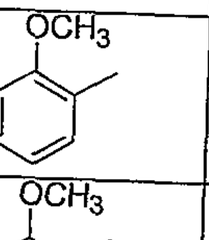
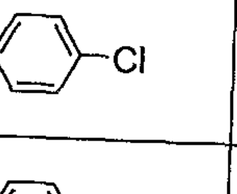
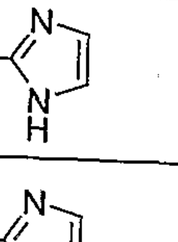
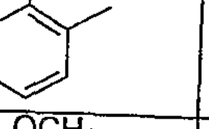
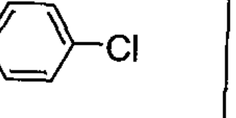
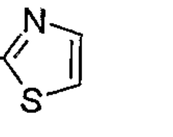
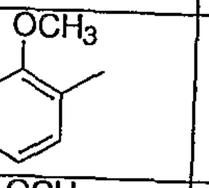
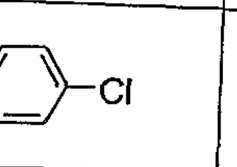
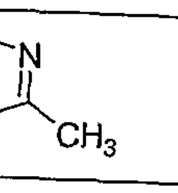
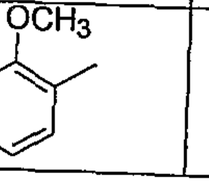
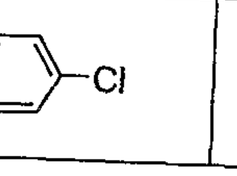
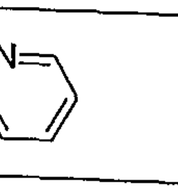
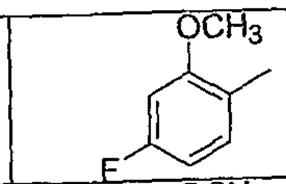
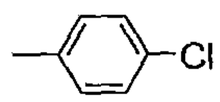
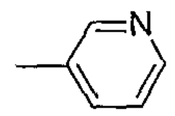
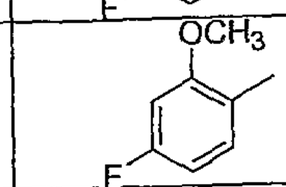
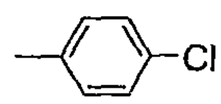
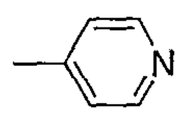
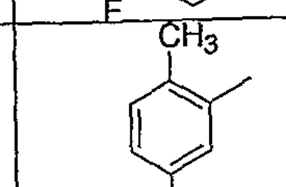
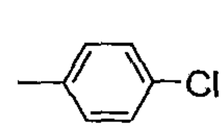
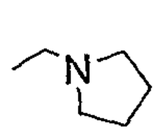
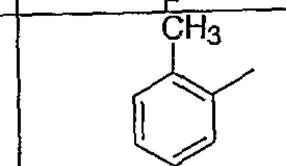
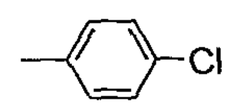
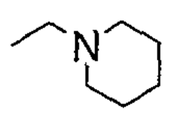
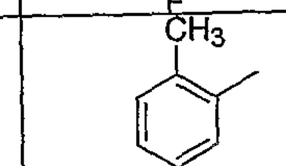
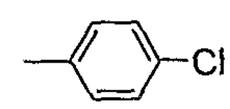
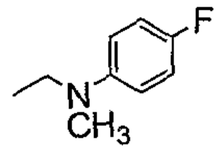
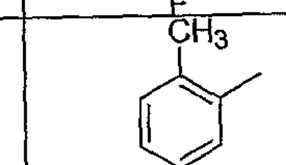
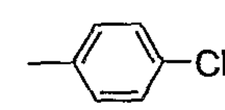
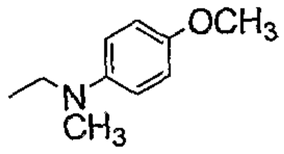
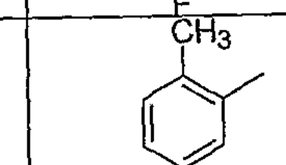
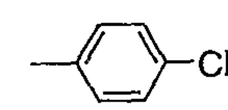
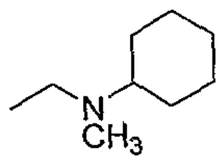
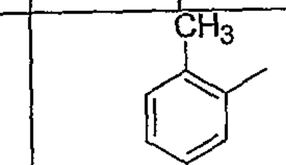
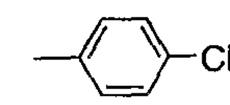
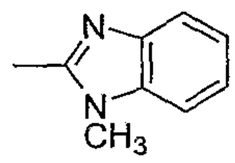
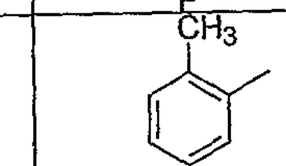
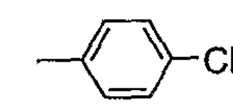
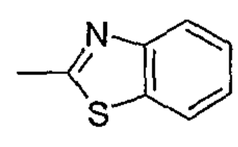
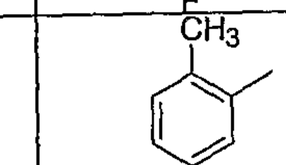
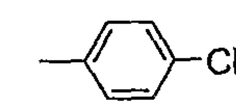
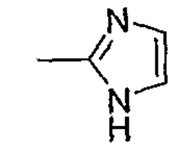
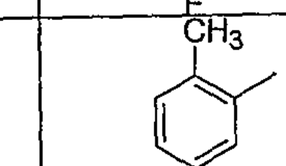
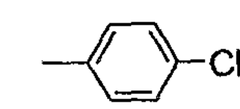
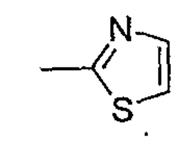
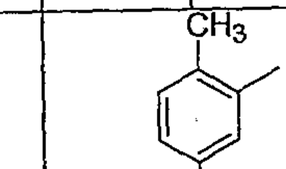
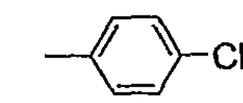
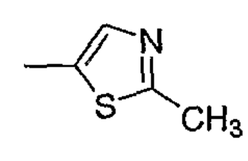
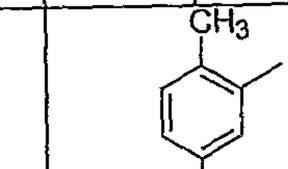
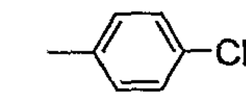
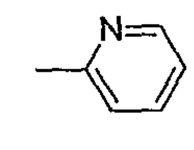
E58			
E59			
E60			

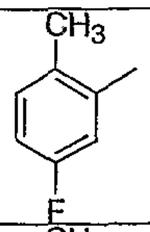
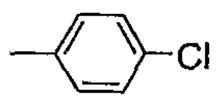
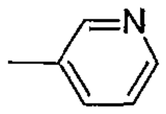
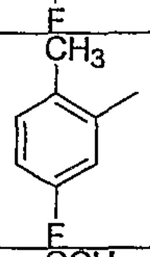
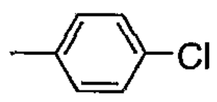
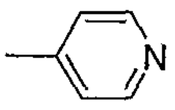
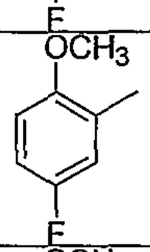
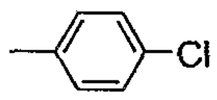
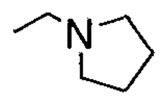
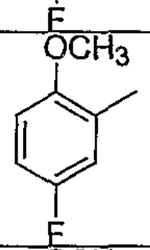
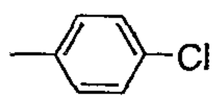
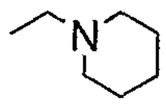
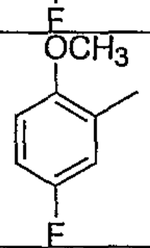
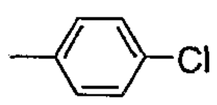
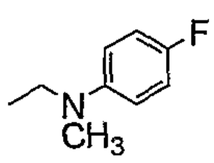
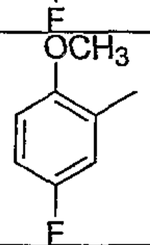
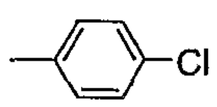
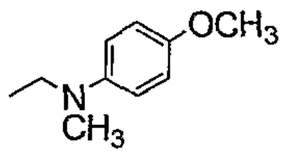
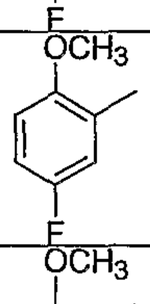
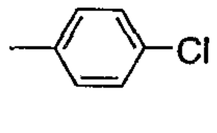
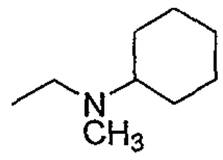
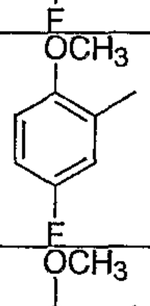
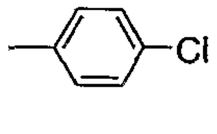
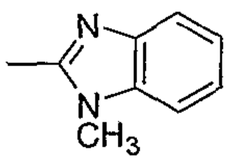
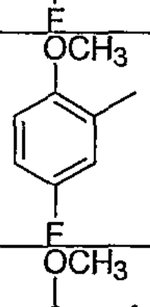
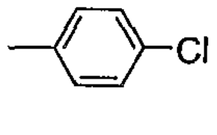
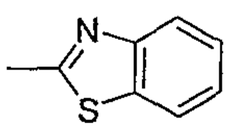
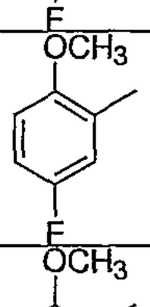
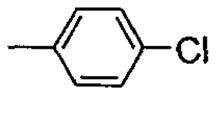
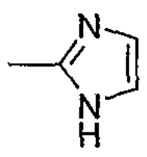
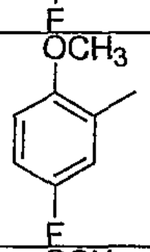
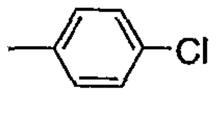
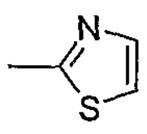
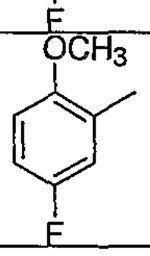
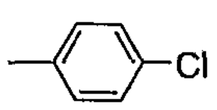
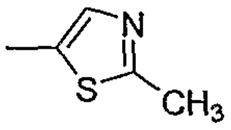
E61			
E62			
E63			
E64			
E65			
E66			
E67			
E68			
E69			
E70			
E71			
E72			
E73			
E74			

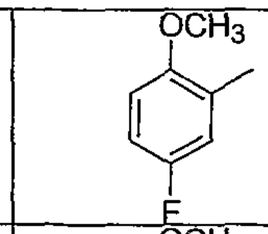
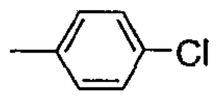
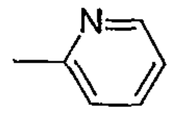
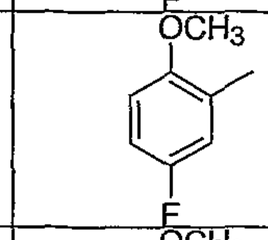
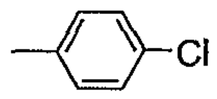
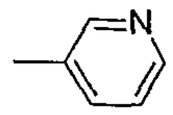
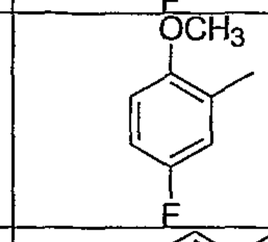
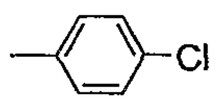
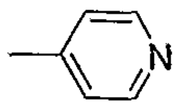
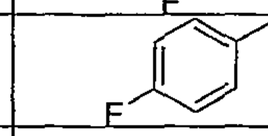
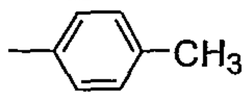
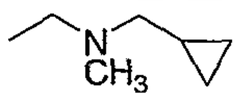
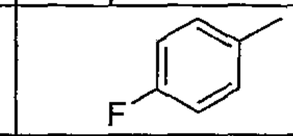
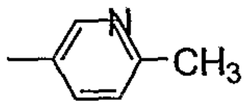
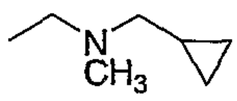
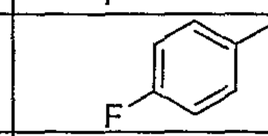
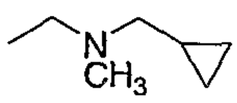
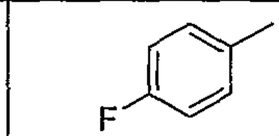
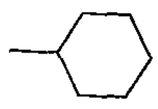
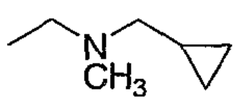
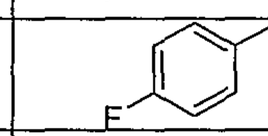
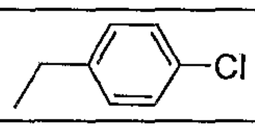
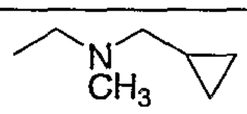
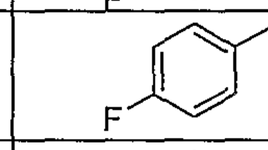
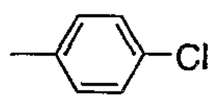
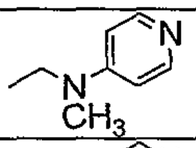
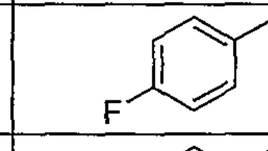
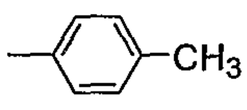
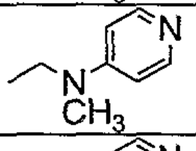
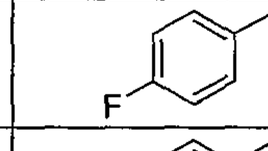
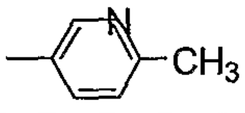
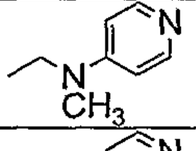
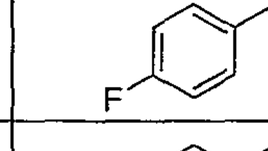
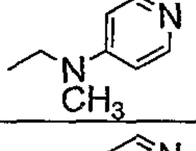
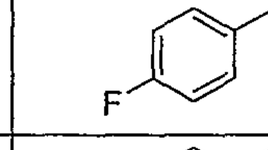
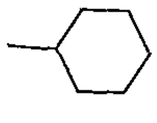
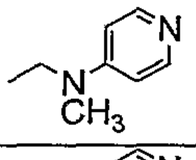
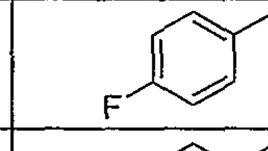
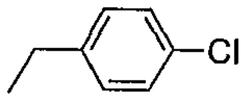
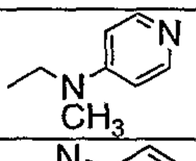
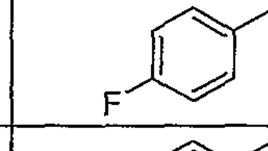
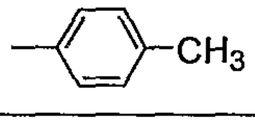
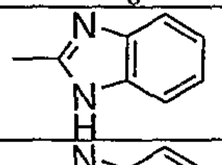
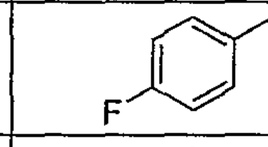
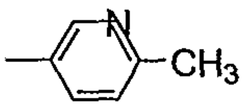
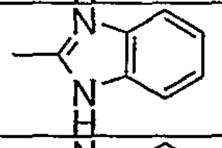
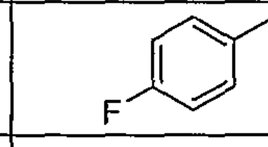
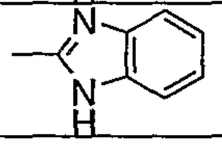
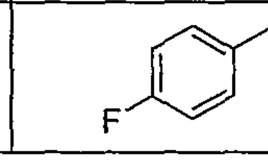
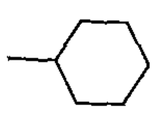
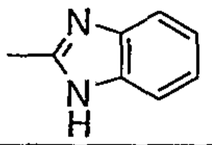
E75			
E76			
E77			
E78			
E79			
E80			
E81			
E82			
E83			
E84			
E85			
E86			
E87			
E88			
E89			
E90			
E91			
E92			

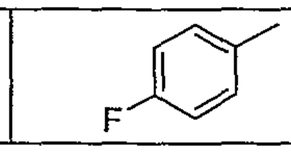
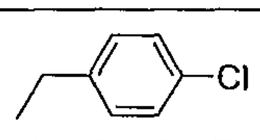
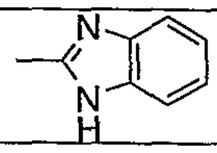
E93			
E94			
E95			
E96			
E97			
E98			
E99			
E100			
E101			
E102			
E103			
E104			
E105			
E106			
E107			
E108			
E109			

E110			
E111			
E112			
E113			
E114			
E115			
E116			
E117			
E118			
E119			
E120			
E121			
E122			
E123			
E124			
E125			
E126			

E127			
E128			
E129			
E130			
E131			
E132			
E133			
E134			
E135			
E136			
E137			
E138			
E139			

E140			
E141			
E142			
E143			
E144			
E145			
E146			
E147			
E148			
E149			
E150			
E151			

E152			
E153			
E154			
E155			
E156			
E157		CH_3	
E158			
E159			
E160			
E161			
E162			
E163		CH_3	
E164			
E165			
E166			
E167			
E168		CH_3	
E169			

E170			

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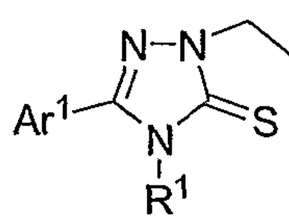

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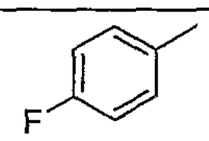
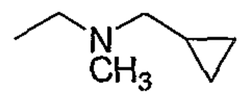
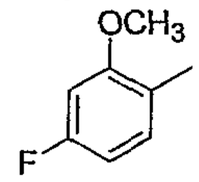
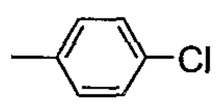
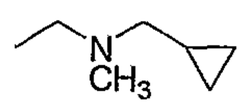
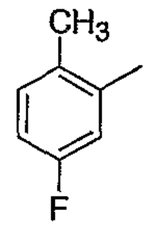
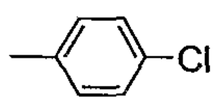
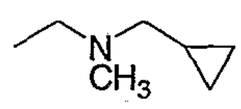
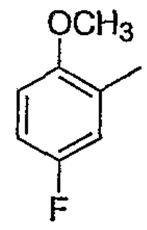
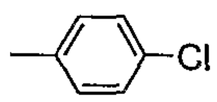
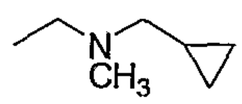
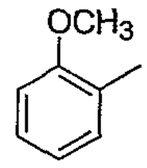
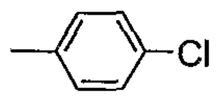
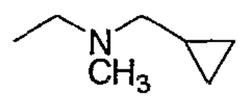
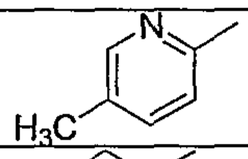
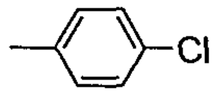
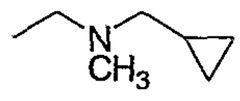
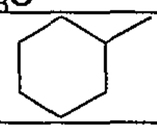
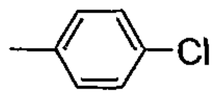
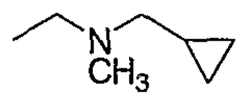
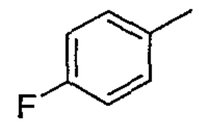
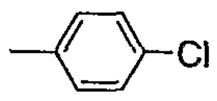
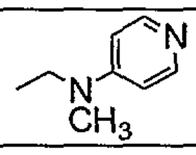
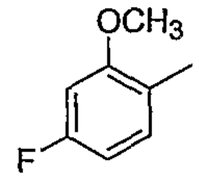
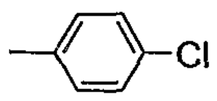
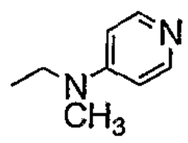
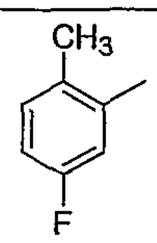
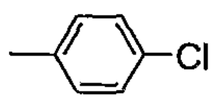
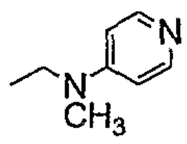
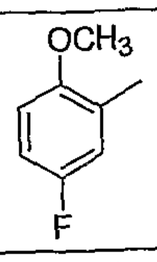
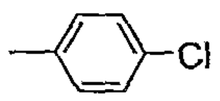
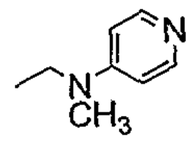
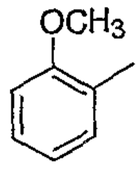
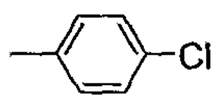
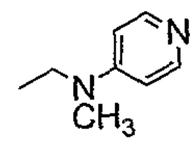
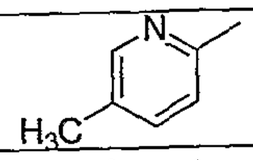
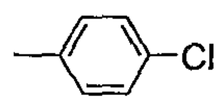
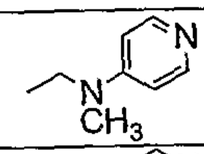
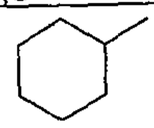
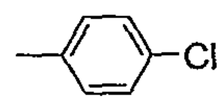
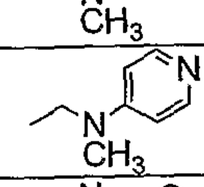
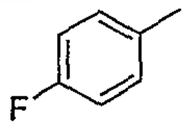
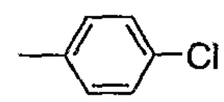
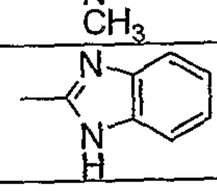
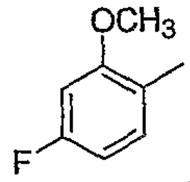
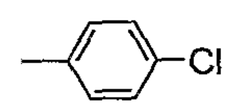
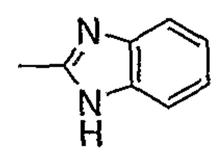
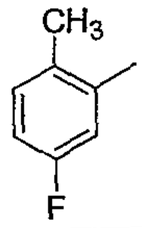
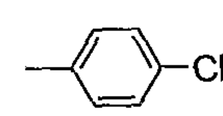
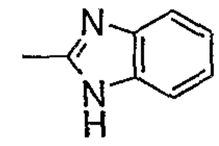
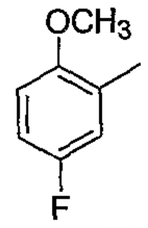
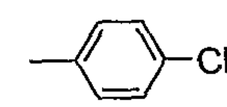
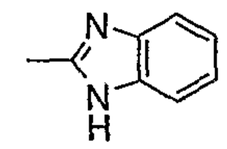
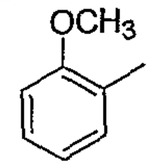
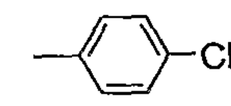
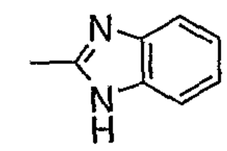
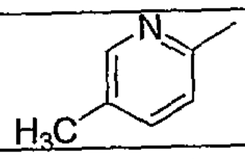
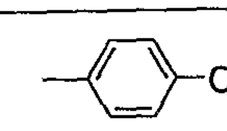
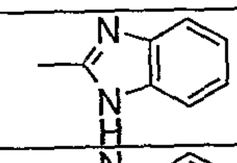
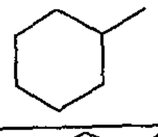
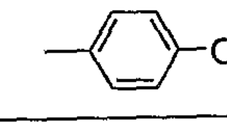
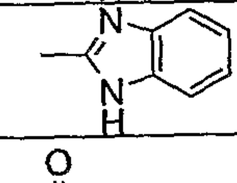
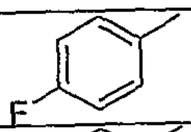
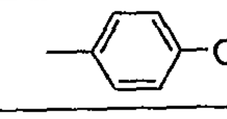
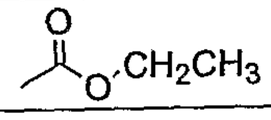
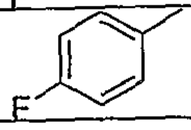
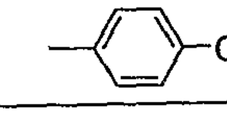
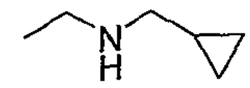
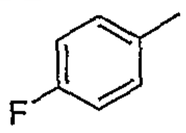
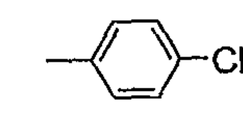
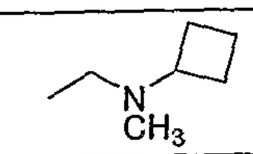
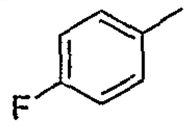
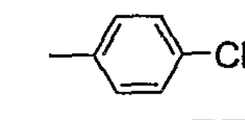
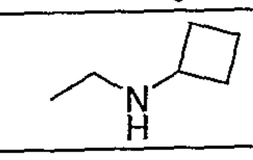
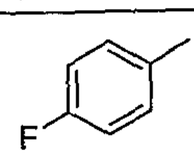
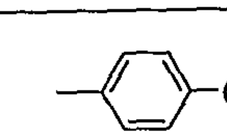
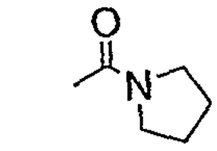
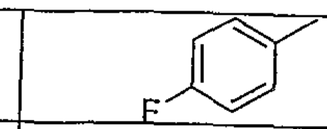
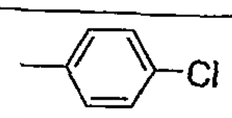
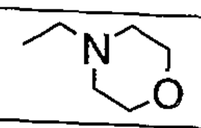
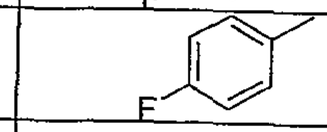
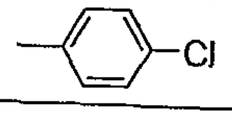
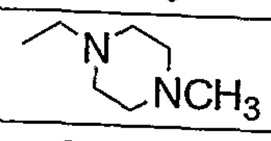
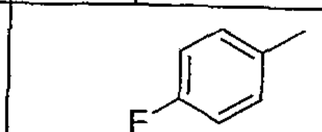
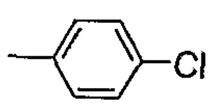
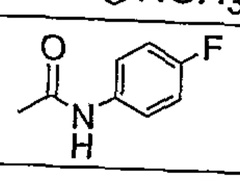
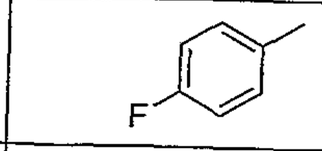
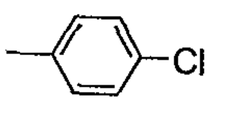
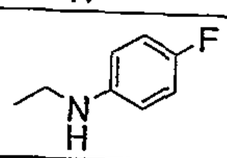
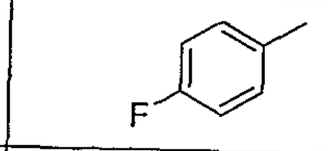
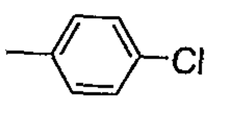
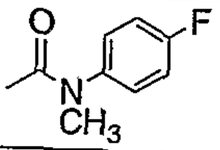
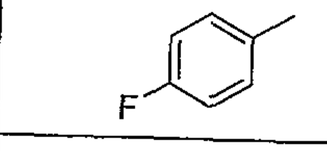
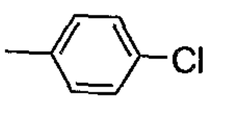
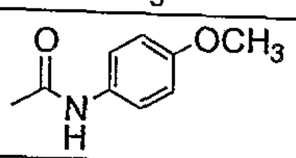
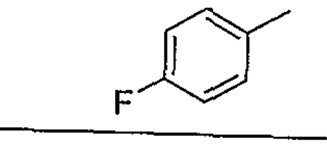
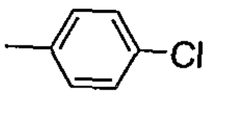
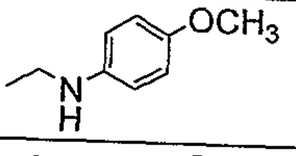
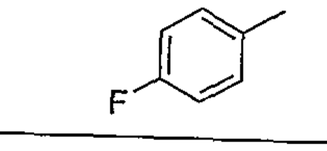
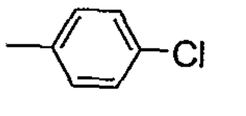
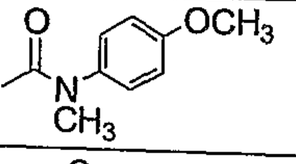
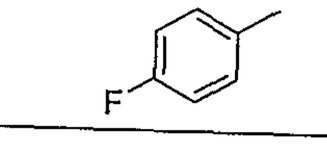
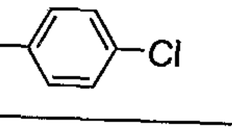
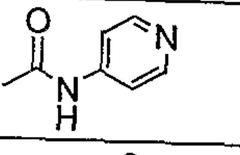
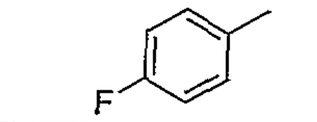
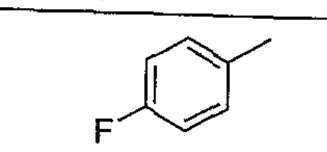
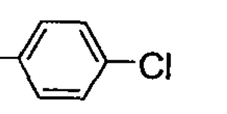
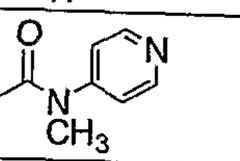
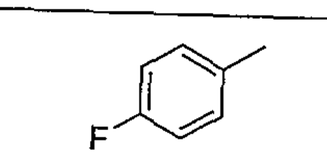
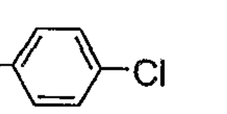
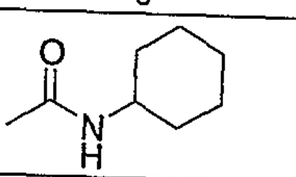
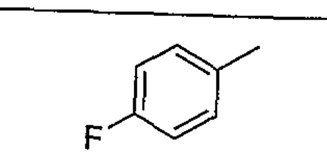
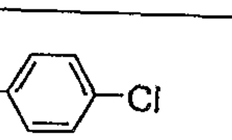
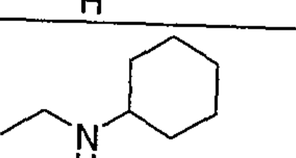
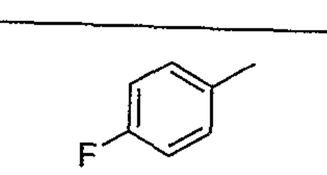
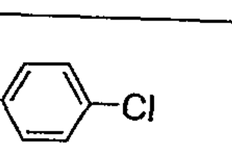
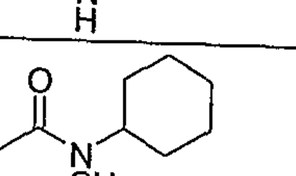
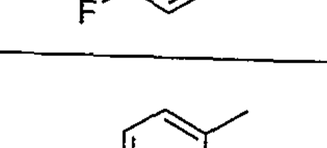
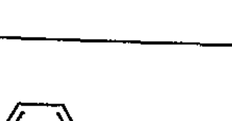
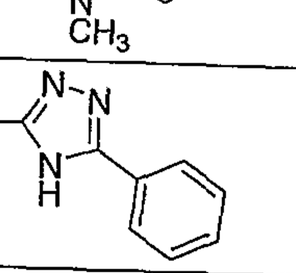
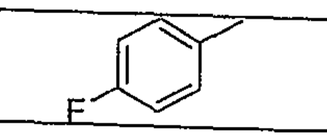
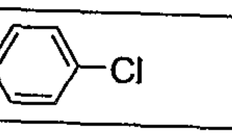
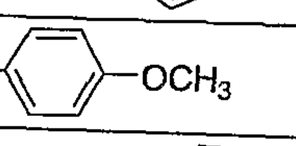
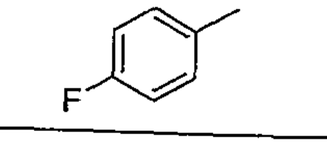
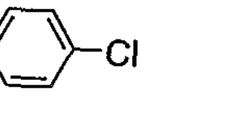
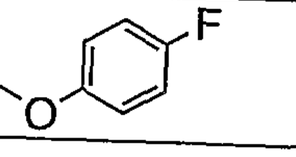
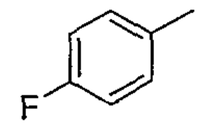
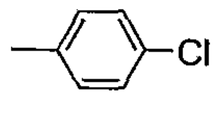
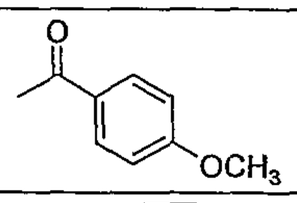
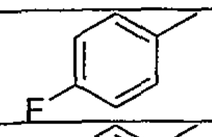
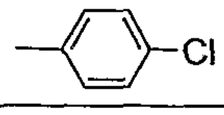
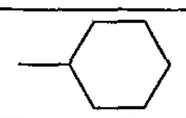
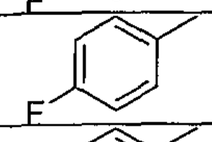
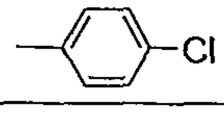
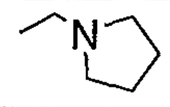
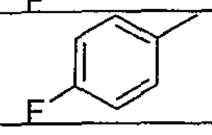
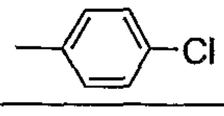
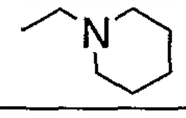
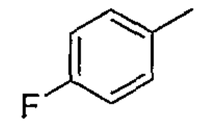
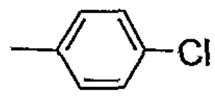
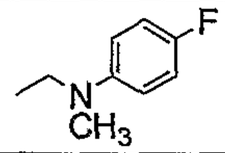
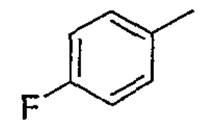
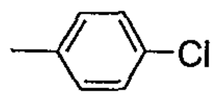
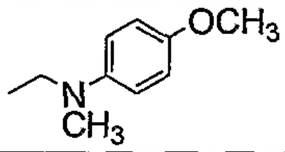
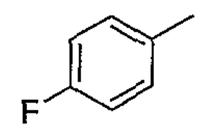
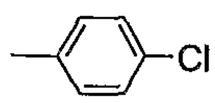
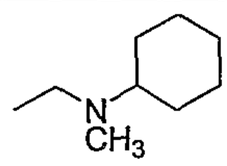
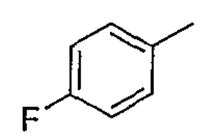
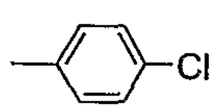
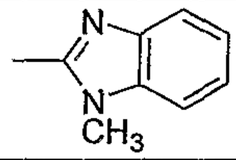
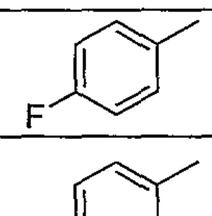
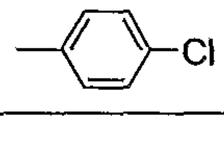
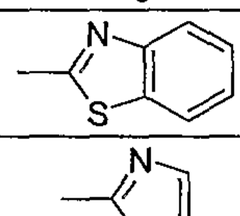
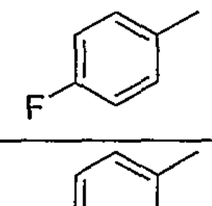
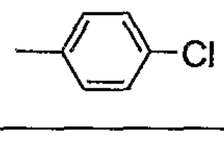
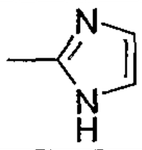
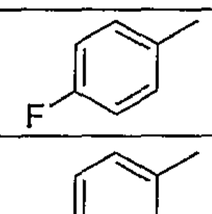
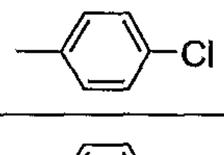
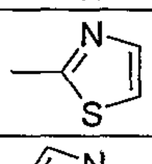
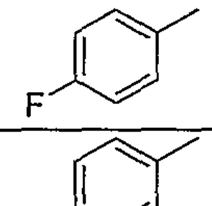
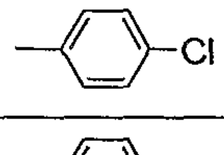
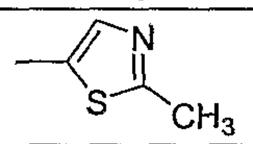
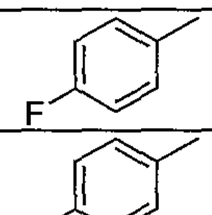
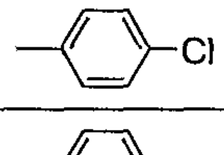
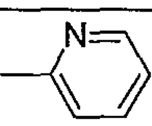
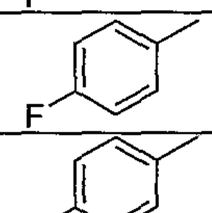
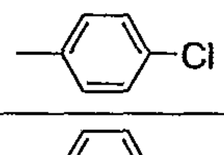
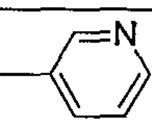
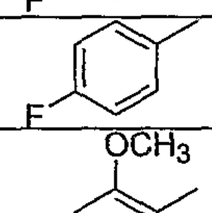
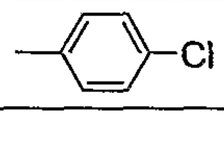
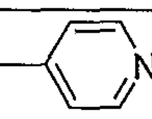
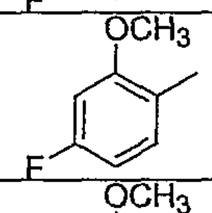
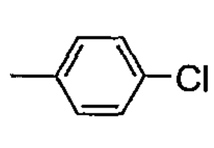
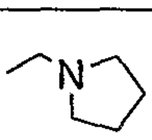
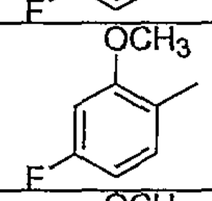
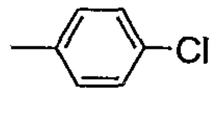
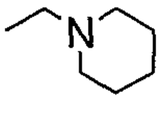
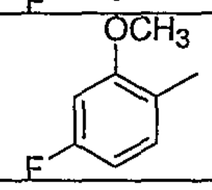
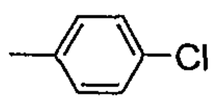
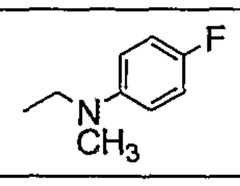
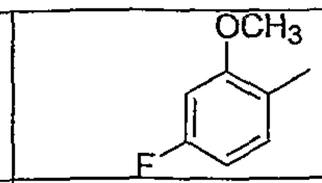
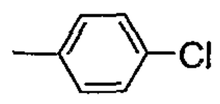
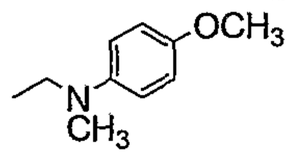
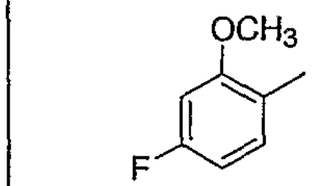
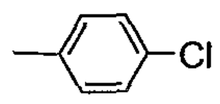
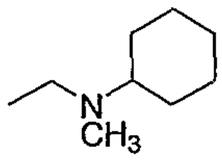
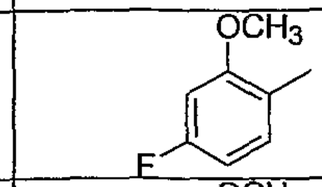
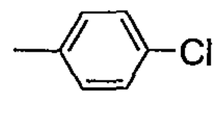
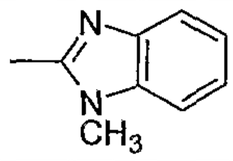
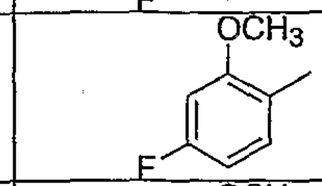
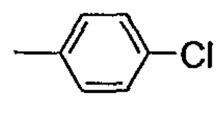
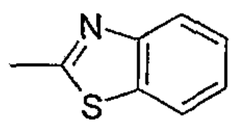
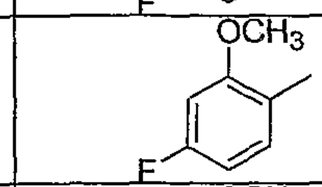
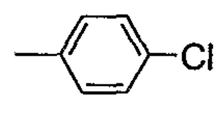
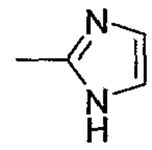
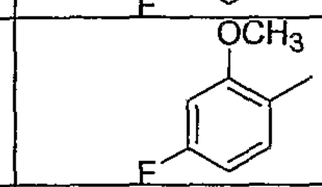
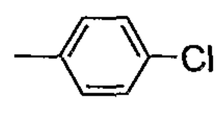
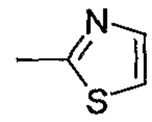
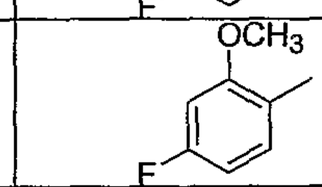
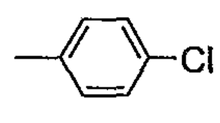
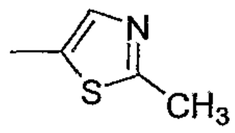
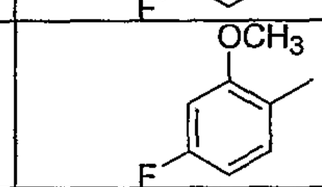
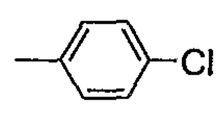
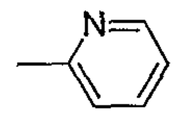
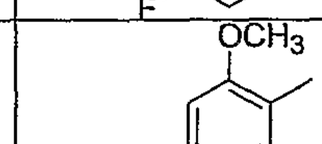
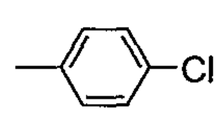
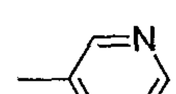
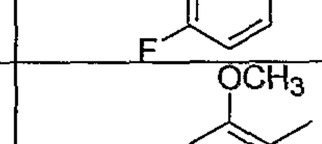
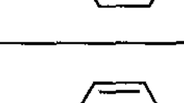
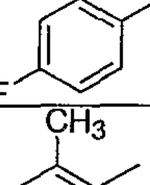
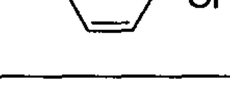
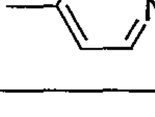
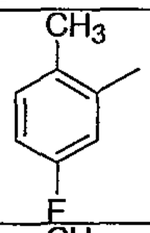
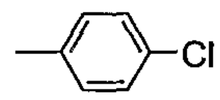
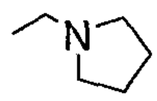
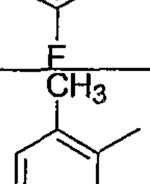
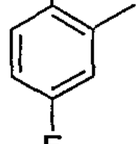
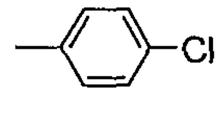
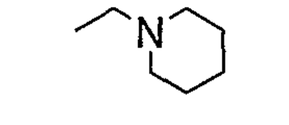
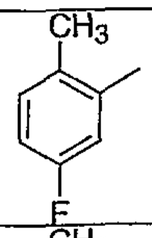
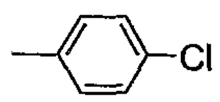
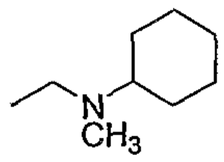
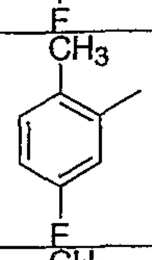
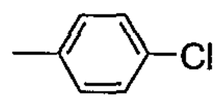
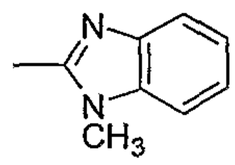
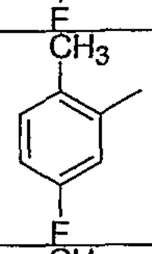
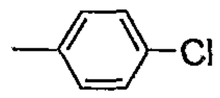
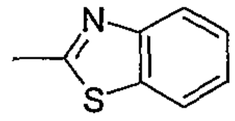
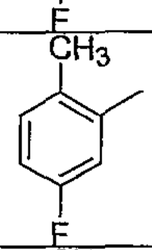
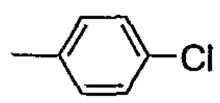
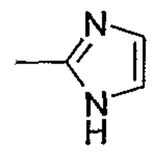
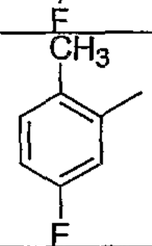
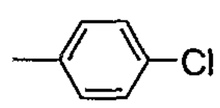
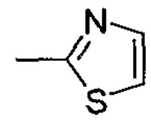
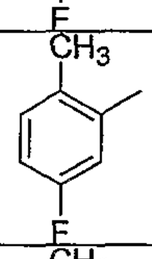
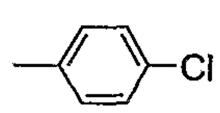
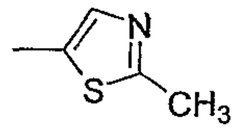
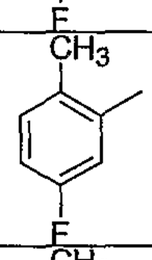
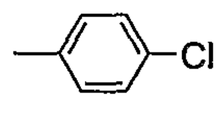
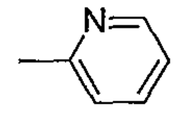
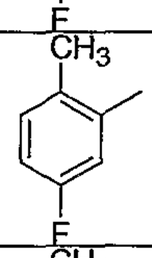
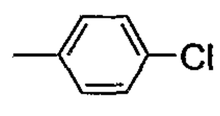
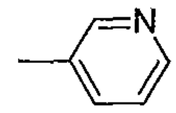
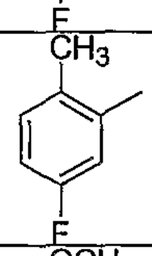
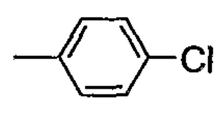
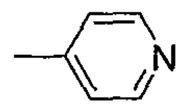
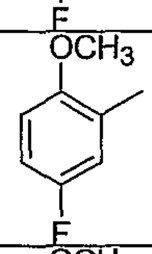
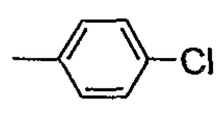
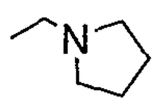
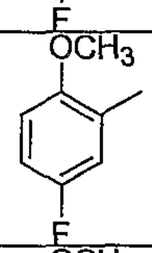
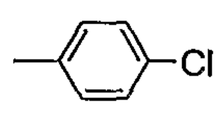
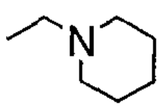
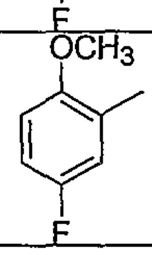
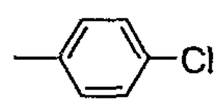
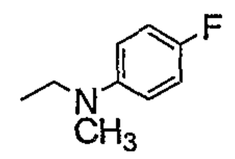
E171		E	
E172			
E173			
E174			
E175			
E176			
E177			
E178			
E179			
E180			

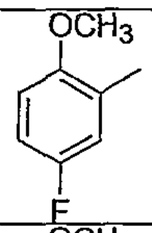
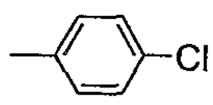
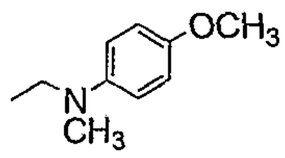
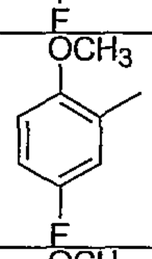
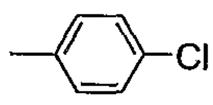
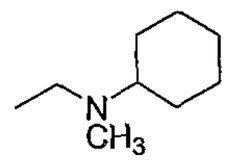
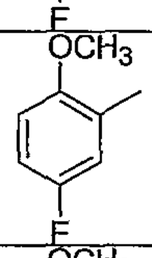
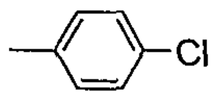
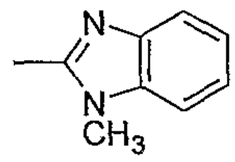
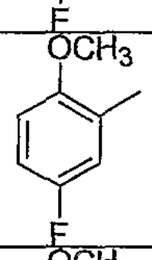
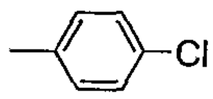
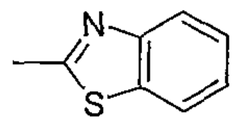
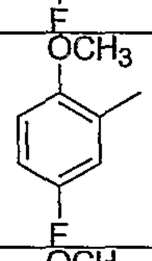
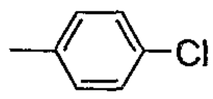
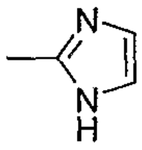
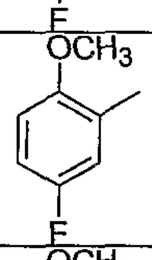
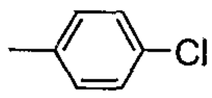
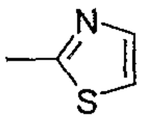
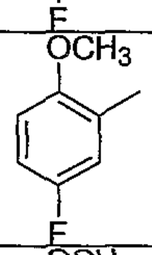
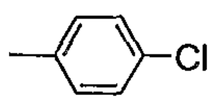
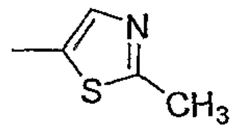
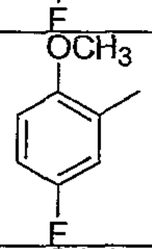
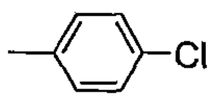
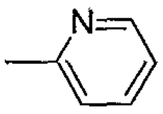
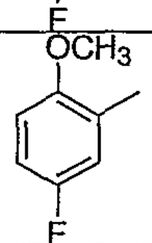
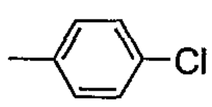
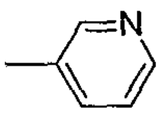
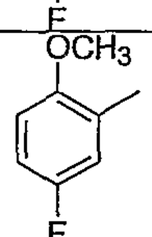
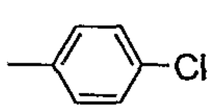
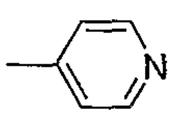
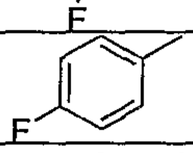
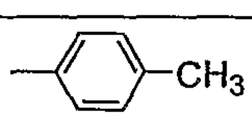
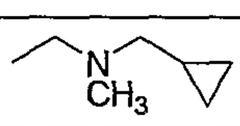
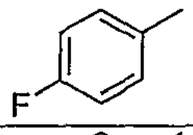
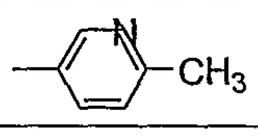
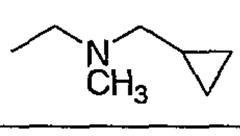
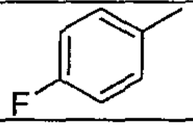
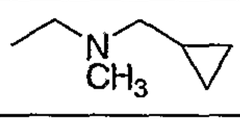
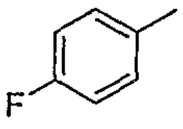
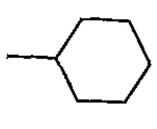
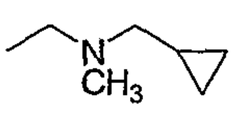
E181			
E182			
E183			
E184			
E185			
E186			
E187			
E188			
E189			
E190			
E191			
E192			
E193			
E194			
E195			
E196			

E197			
E198			
E199			
E200			
E201			
E202			
E203			
E204			
E205			
E206			
E207			
E208			
E209			
E210			
E211			
E212			
E213			

E214			
E215			
E216			
E217			
E218			
E219			
E220			
E221			
E222			
E223			
E224			
E225			
E226			
E227			
E228			
E229			
E230			
E231			

E232			
E233			
E234			
E235			
E236			
E237			
E238			
E239			
E240			
E241			
E242			
E243			
E244			
E245			

E246			
E247			
E248			
E249			
E250			
E251			
E252			
E253			
E254			
E255			
E256			
E257			

E258			
E259			
E260			
E261			
E262			
E263			
E264			
E265			
E266			
E267			
E268			
E269			
E270		CH_3	
E271			

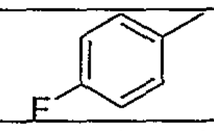
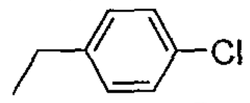
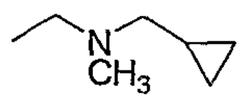
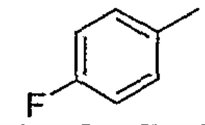
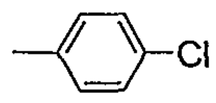
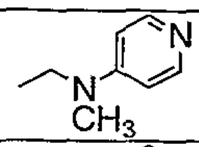
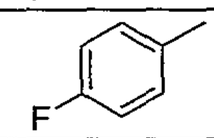
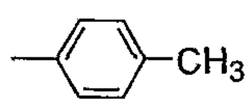
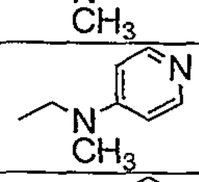
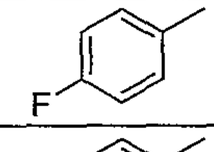
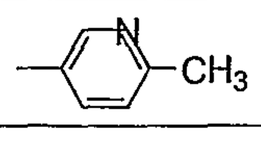
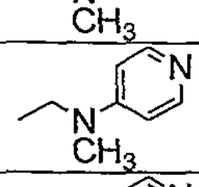
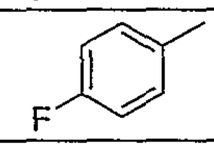
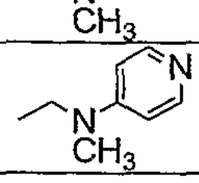
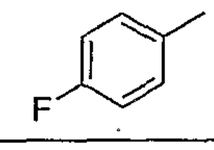
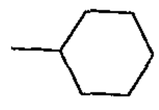
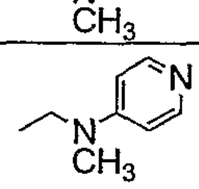
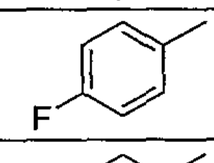
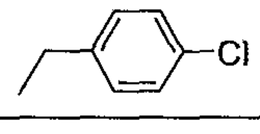
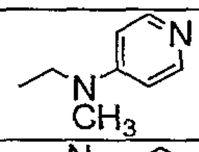
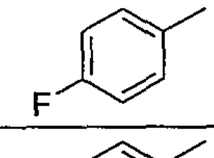
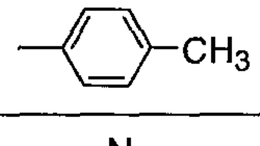
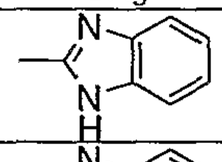
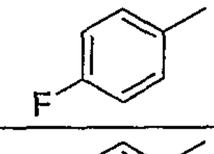
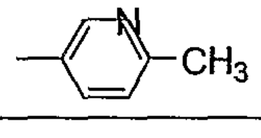
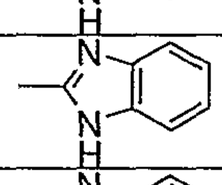
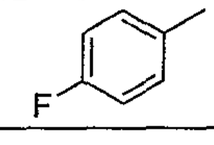
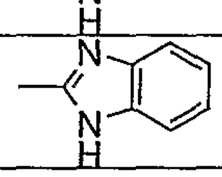
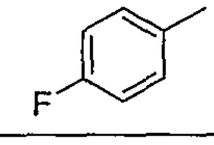
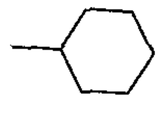
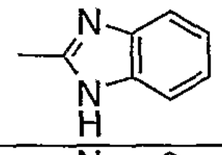
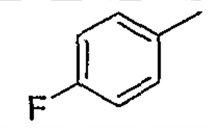
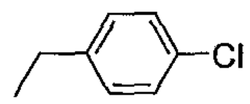
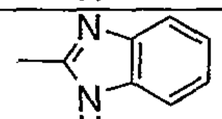
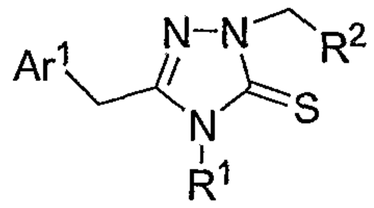
E272			
E273			
E274			
E275			
E276		CH_3	
E277			
E278			
E279			
E280			
E281		CH_3	
E282			
E283			

TABLE E-1D



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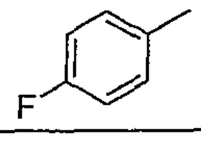
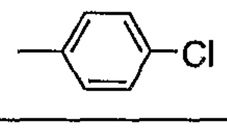
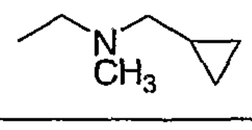
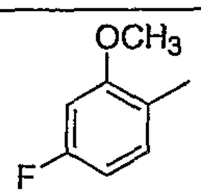
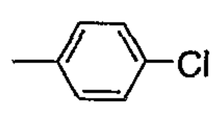
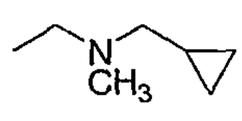
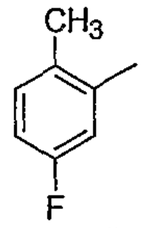
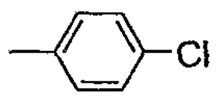
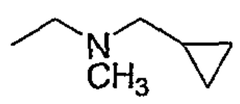
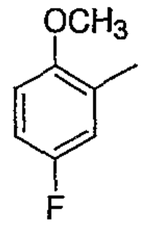
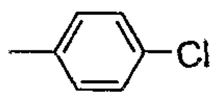
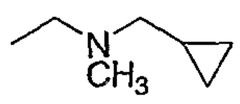
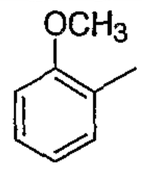
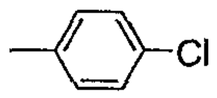
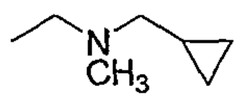
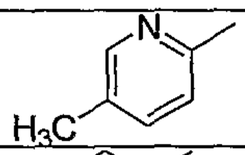
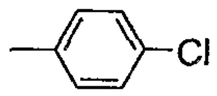
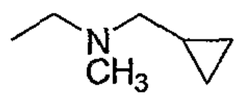
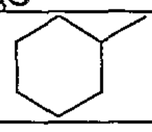
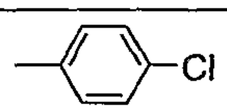
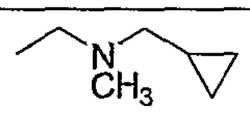
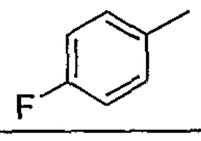
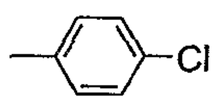
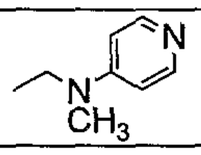
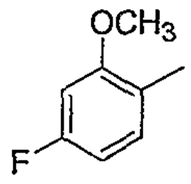
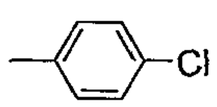
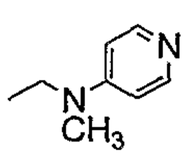
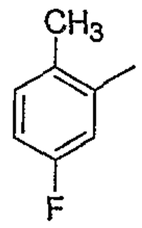
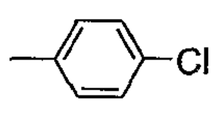
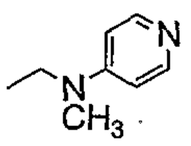
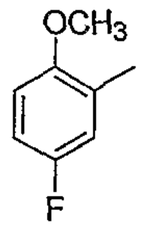
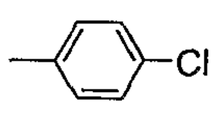
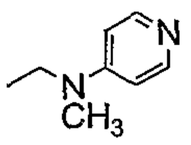
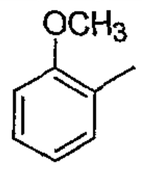
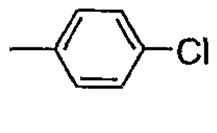
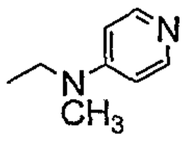
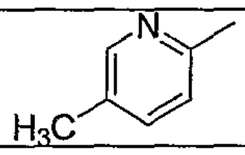
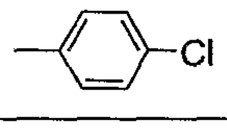
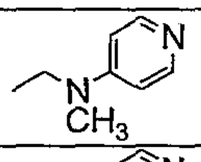
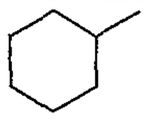
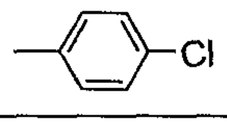
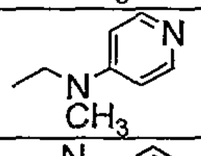
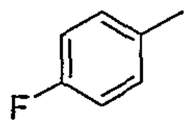
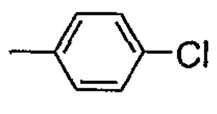
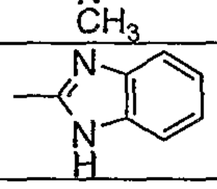
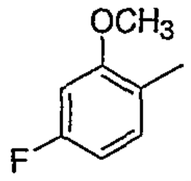
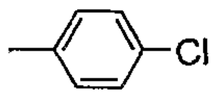
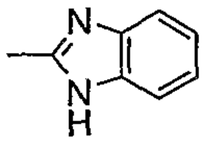
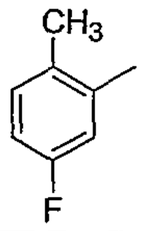
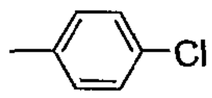
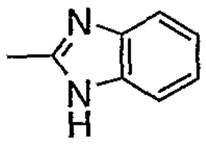
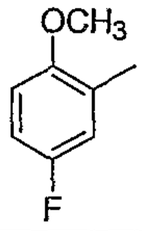
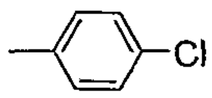
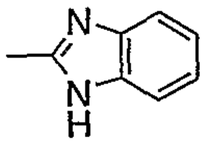
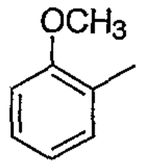
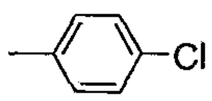
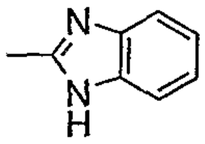
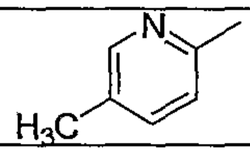
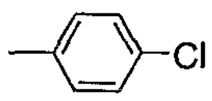
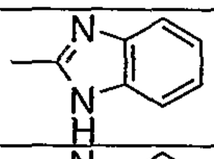
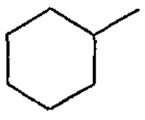
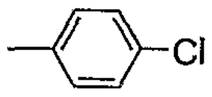
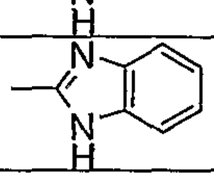
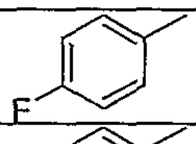
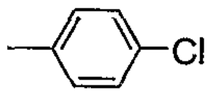
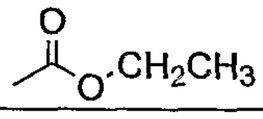
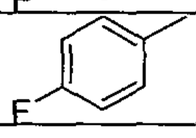
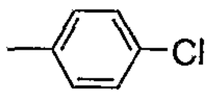
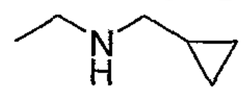
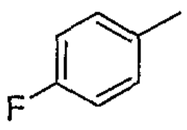
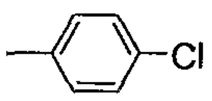
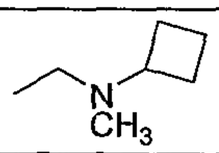
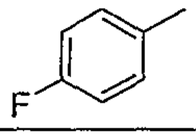
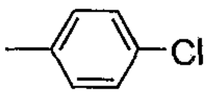
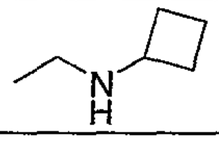
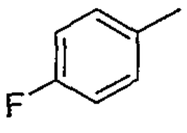
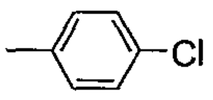
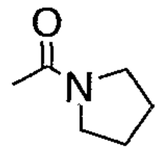
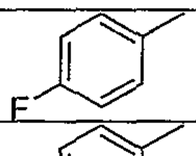
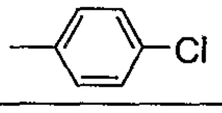
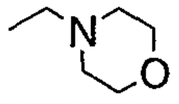
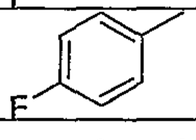
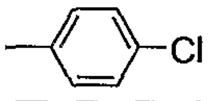
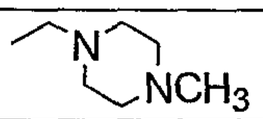
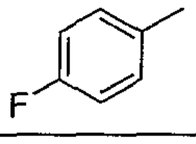
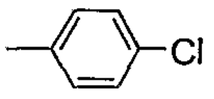
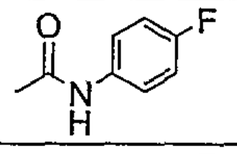
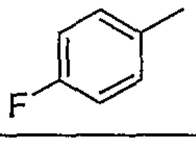
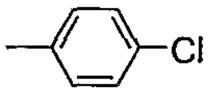
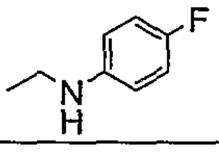
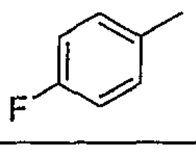
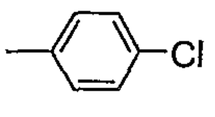
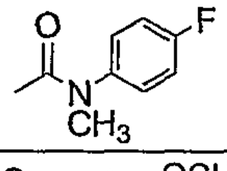
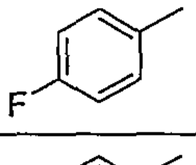
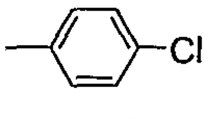
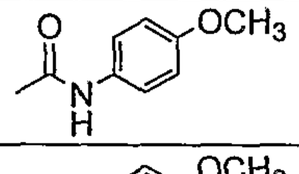
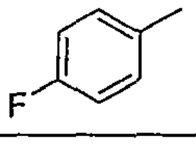
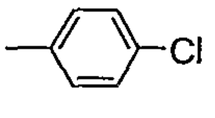
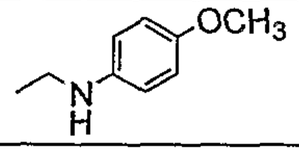
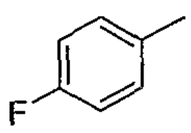
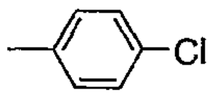
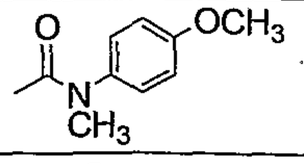
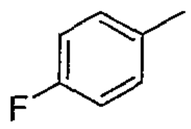
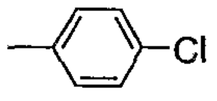
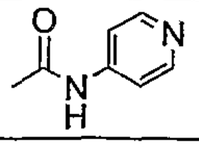
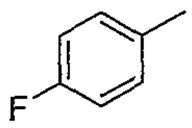
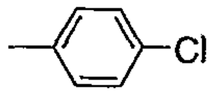
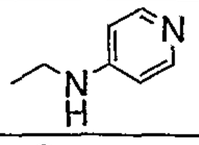
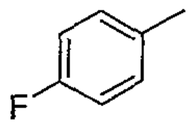
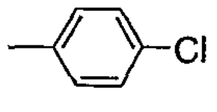
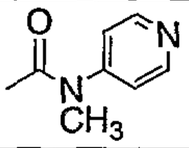
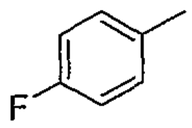
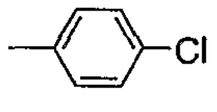
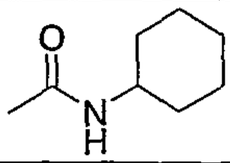
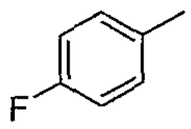
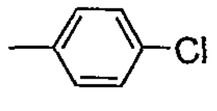
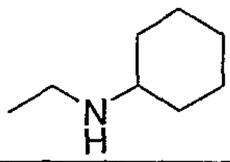
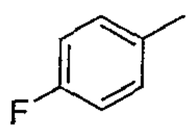
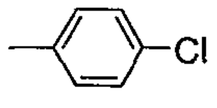
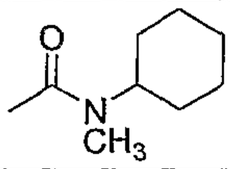
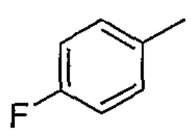
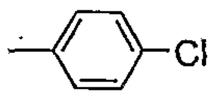
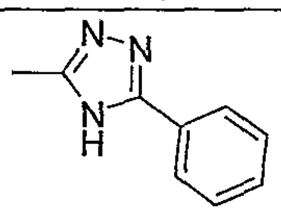
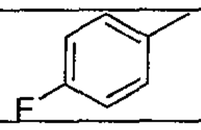
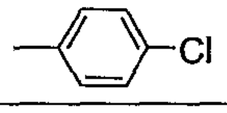
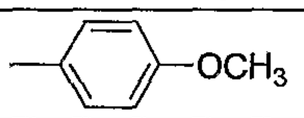
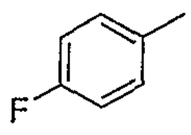
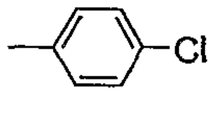
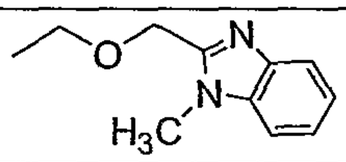
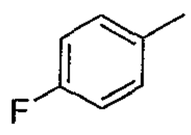
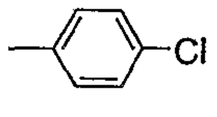
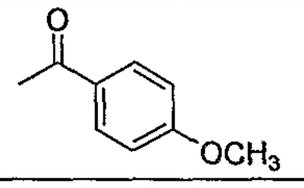
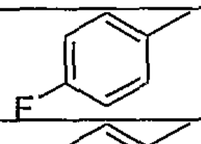
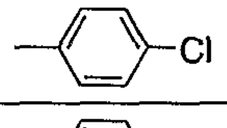
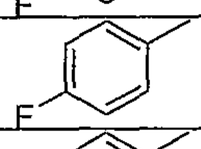
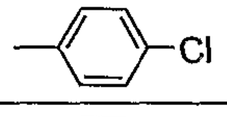
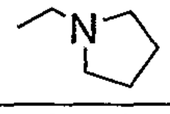
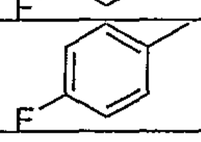
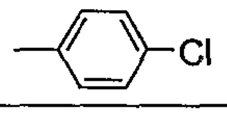
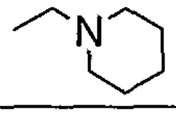
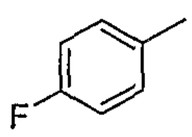
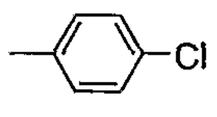
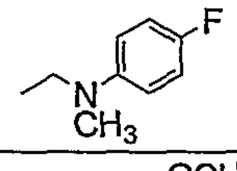
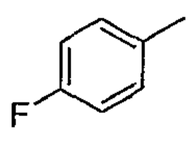
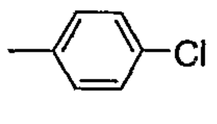
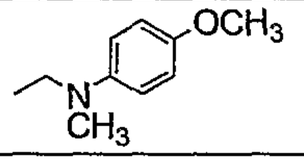
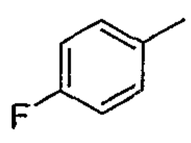
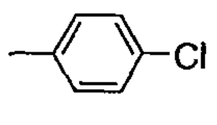
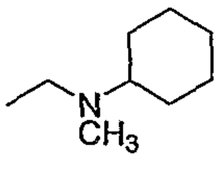
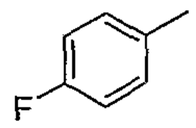
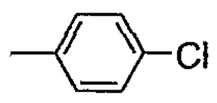
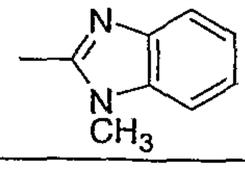
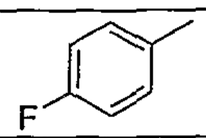
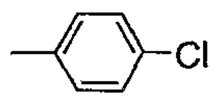
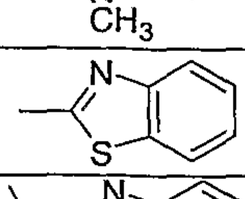
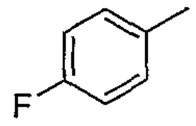
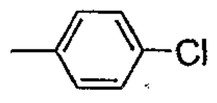
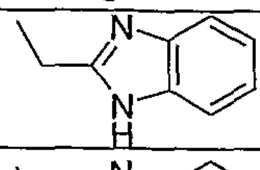
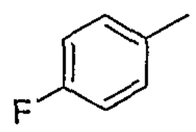
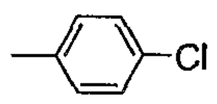
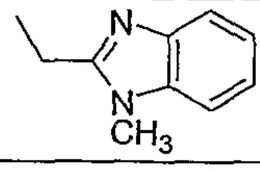
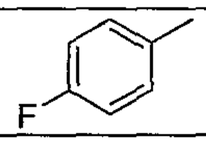
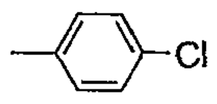
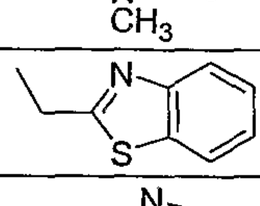
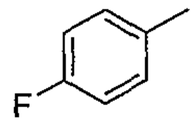
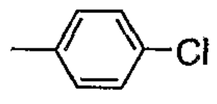
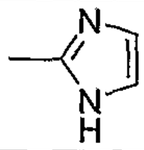
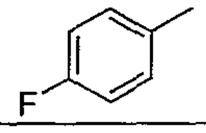
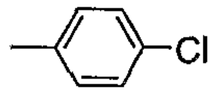
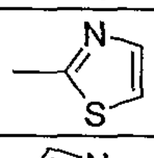
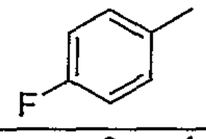
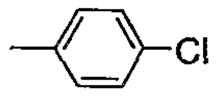
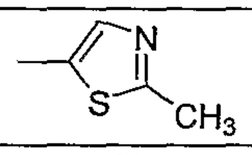
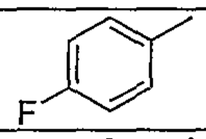
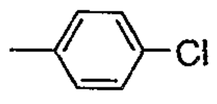
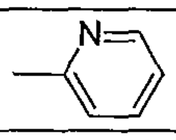
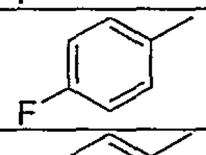
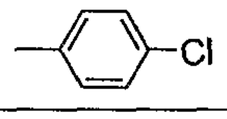
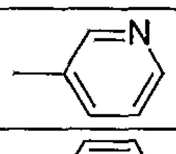
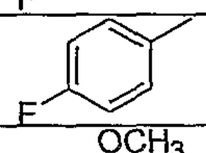
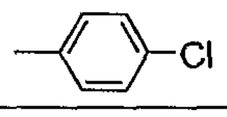
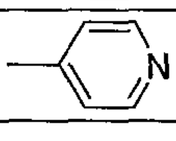
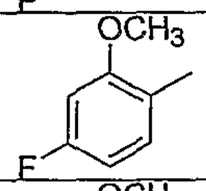
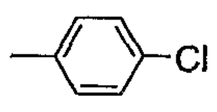
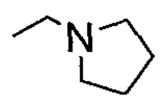
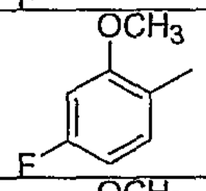
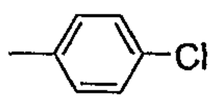
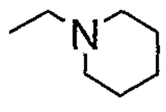
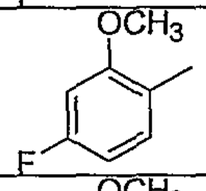
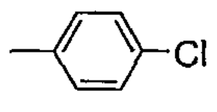
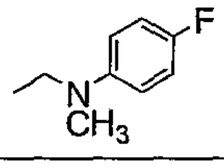
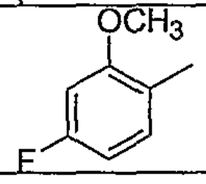
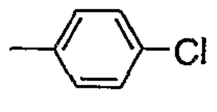
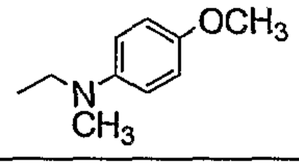
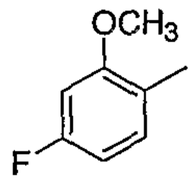
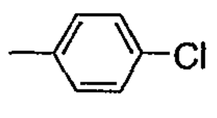
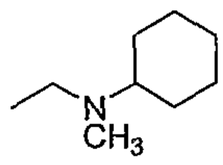
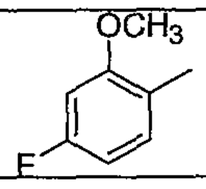
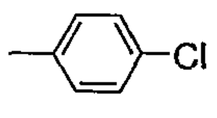
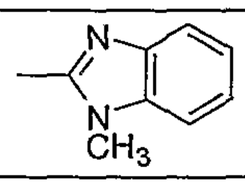
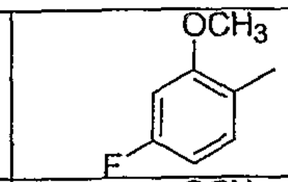
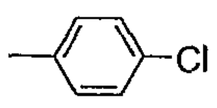
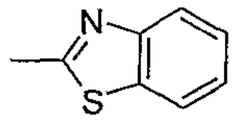
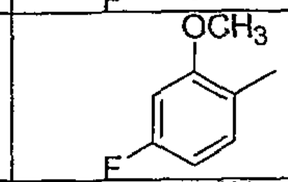
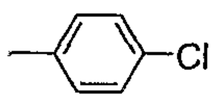
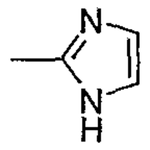
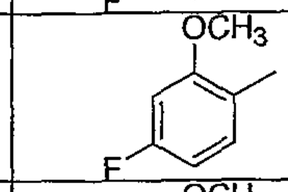
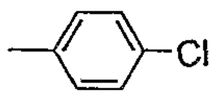
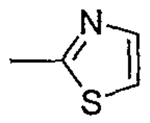
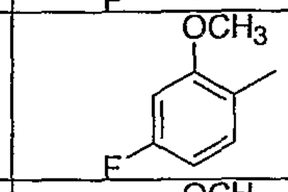
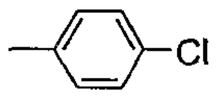
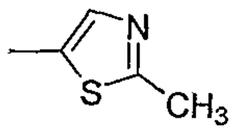
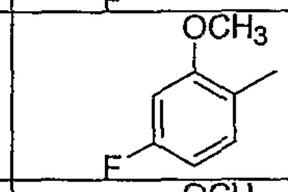
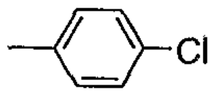
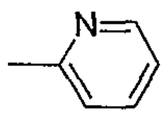
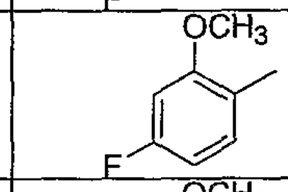
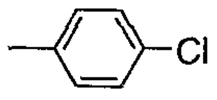
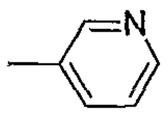
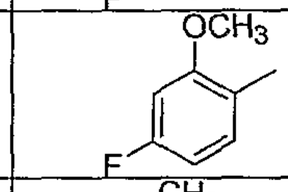
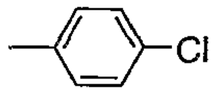
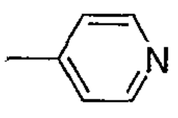
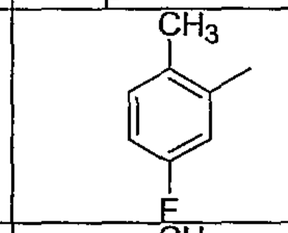
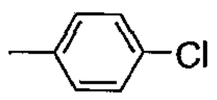
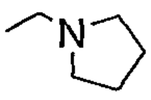
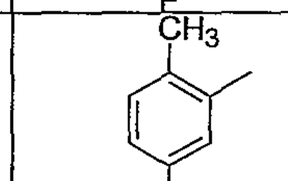
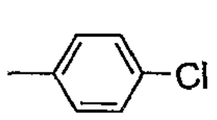
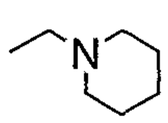
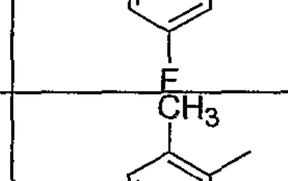
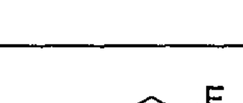
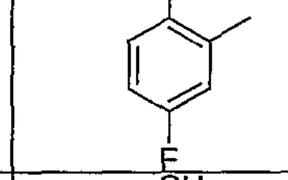
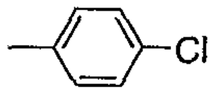
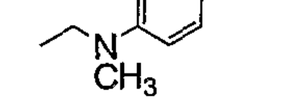
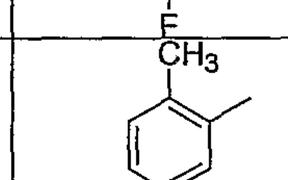
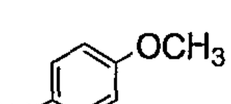
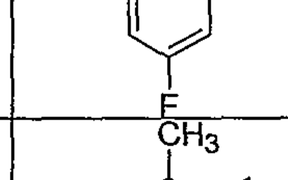
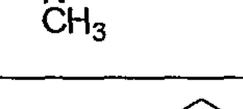
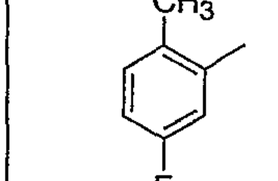
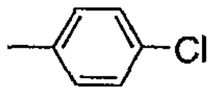
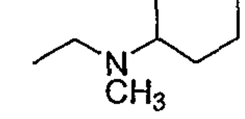
E284			
E285			

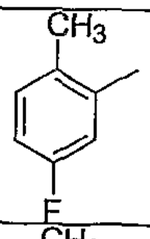
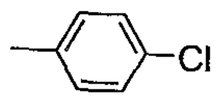
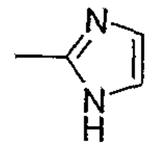
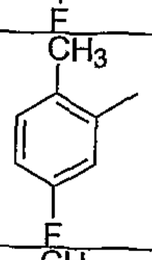
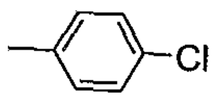
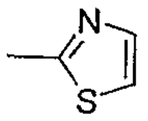
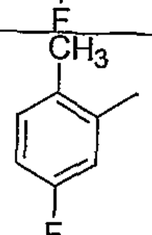
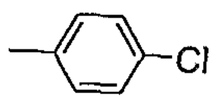
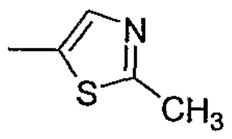
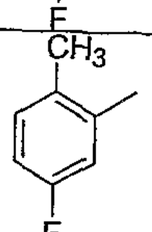
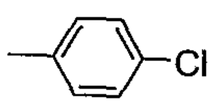
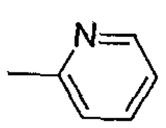
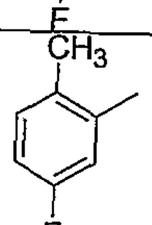
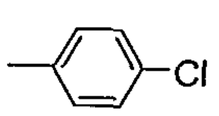
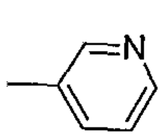
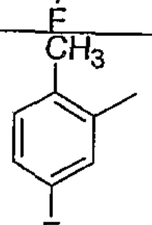
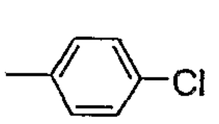
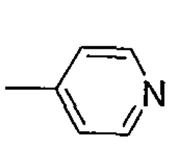
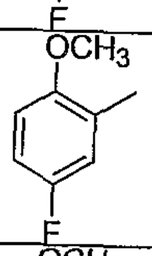
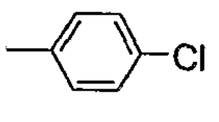
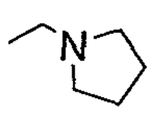
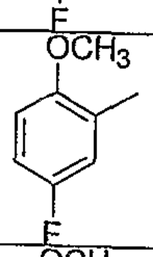
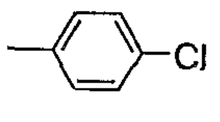
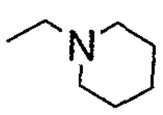
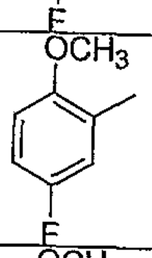
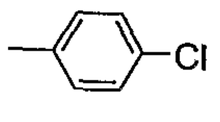
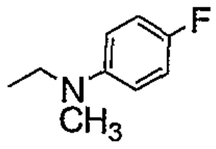
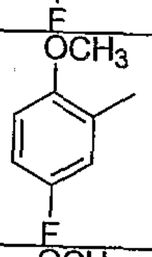
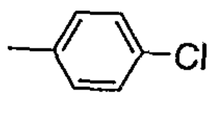
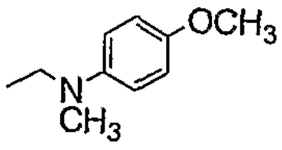
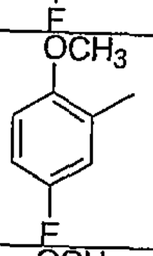
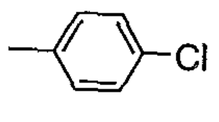
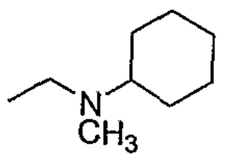
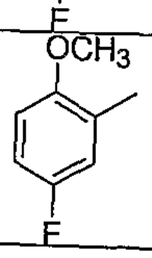
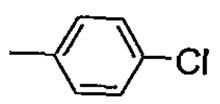
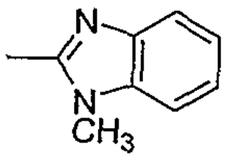
E286			
E287			
E288			
E289			
E290			
E291			
E292			
E293			
E294			
E295			
E296			
E297			
E298			
E299			

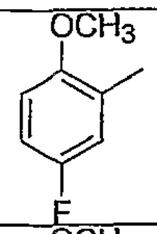
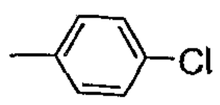
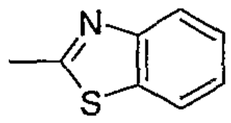
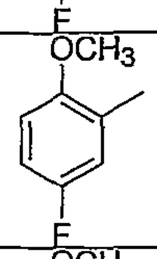
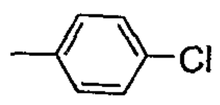
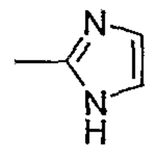
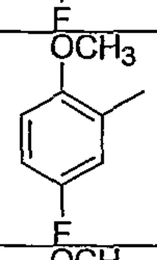
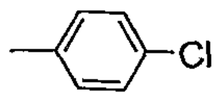
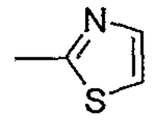
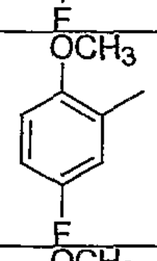
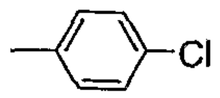
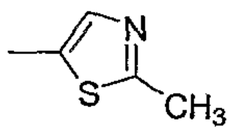
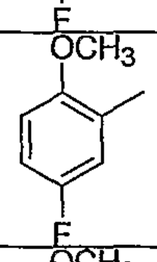
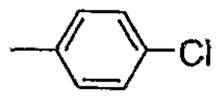
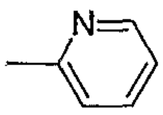
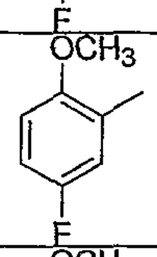
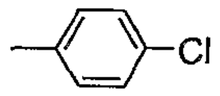
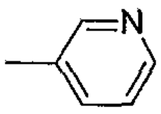
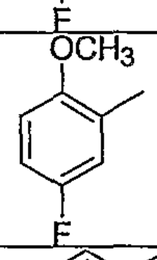
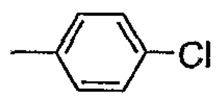
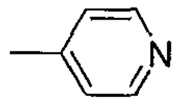
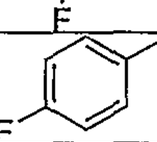
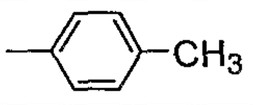
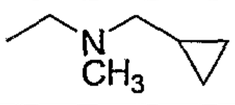
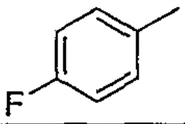
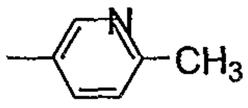
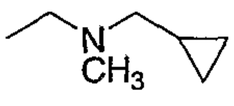
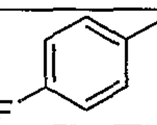
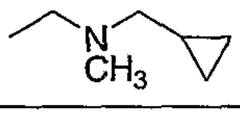
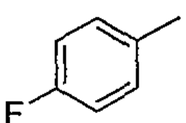
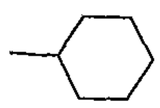
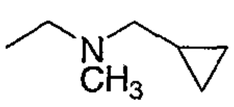
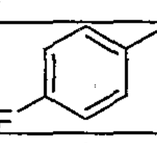
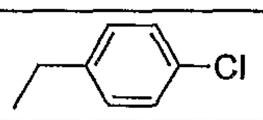
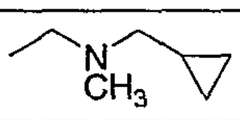
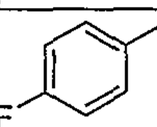
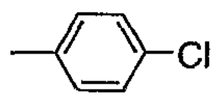
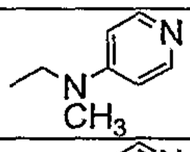
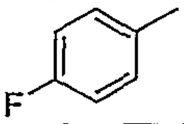
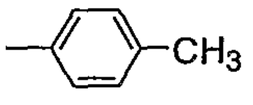
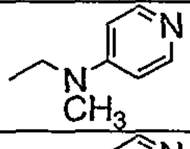
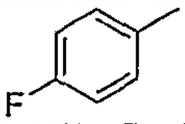
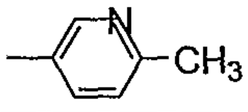
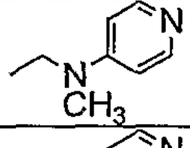
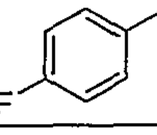
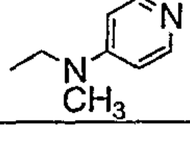
E300			
E301			
E302			
E303			
E304			
E305			
E306			
E307			
E308			
E309			
E310			
E311			
E312			
E313			
E314			
E315			
E316			

E317			
E318			
E319			
E320			
E321			
E322			
E323			
E324			
E325			
E326			
E327			
E328			
E329			
E330			
E331			
E332			
E333			

E334			
E335			
E336			
E337			
E338			
E339			
E340			
E341			
E342			
E343			
E344			
E345			
E346			
E347			
E348			
E349			
E350			

E351			
E352			
E353			
E354			
E355			
E356			
E357			
E358			
E359			
E360			
E361			
E362			
E363			
E364			

E365			
E366			
E367			
E368			
E369			
E370			
E371			
E372			
E373			
E374			
E375			
E376			

E377			
E378			
E379			
E380			
E381			
E382			
E383			
E384			
E385			
E386		CH_3	
E387			
E388			
E389			
E390			
E391			
E392		CH_3	

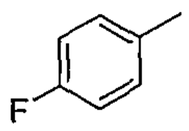
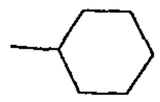
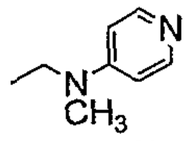
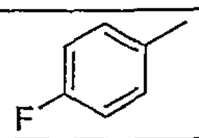
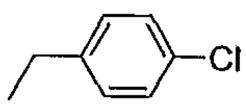
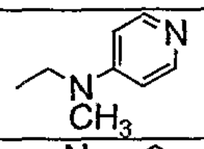
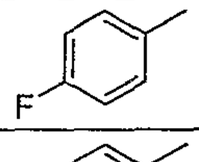
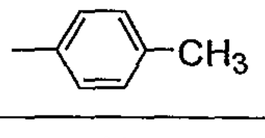
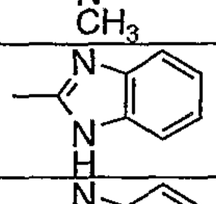
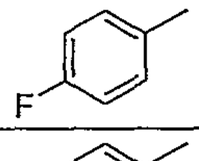
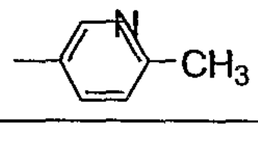
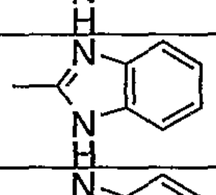
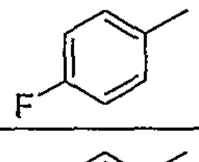
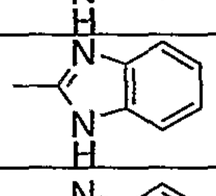
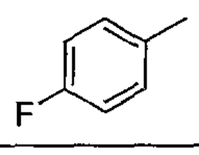
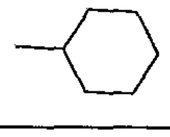
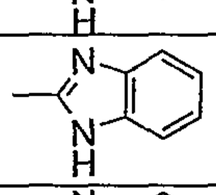
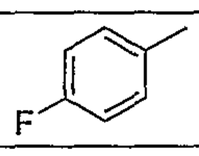
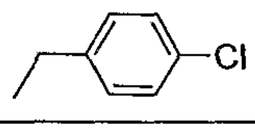
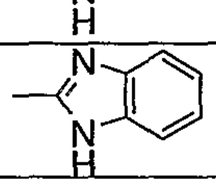
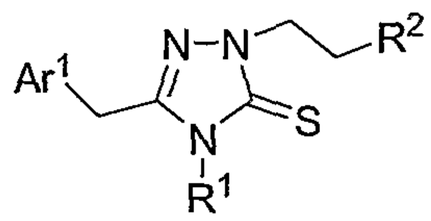
E393			
E394			
E395			
E396			
E397		CH_3	
E398			
E399			

TABLE E-1E



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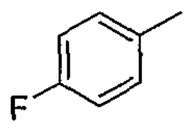
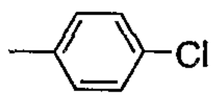
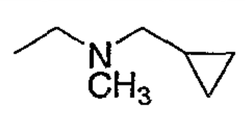
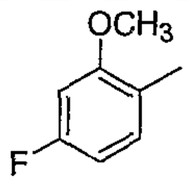
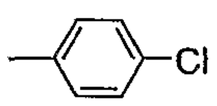
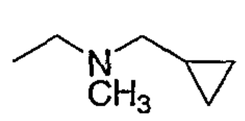
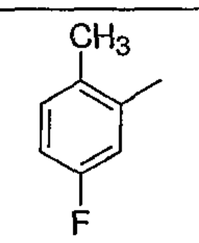
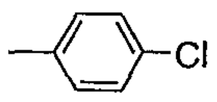
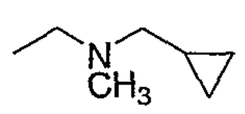
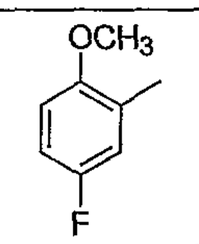
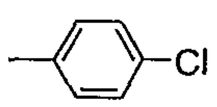
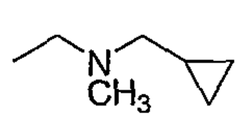
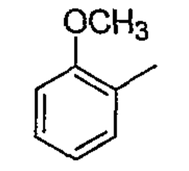
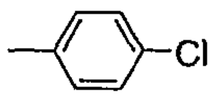
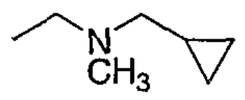
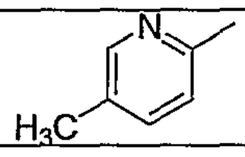
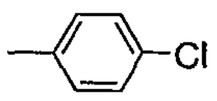
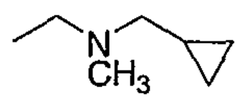
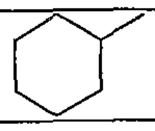
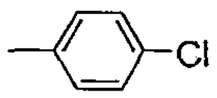
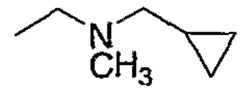
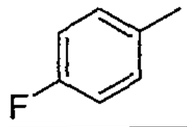
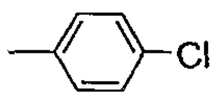
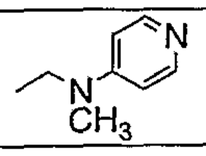
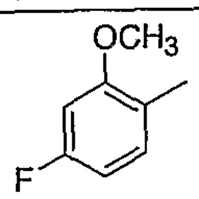
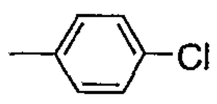
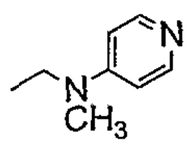
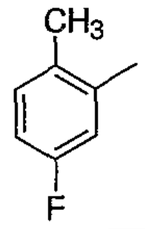
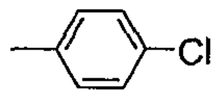
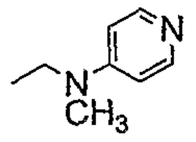
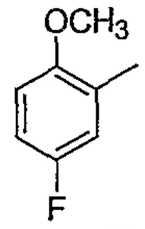
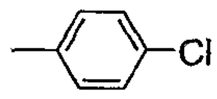
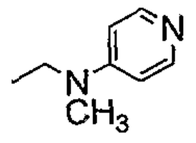
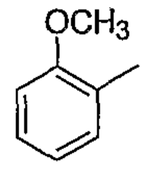
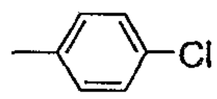
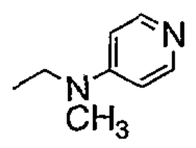
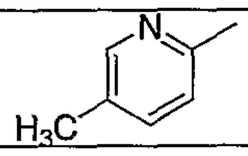
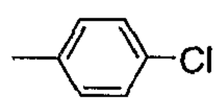
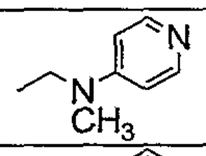
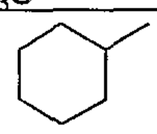
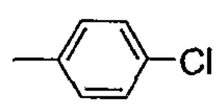
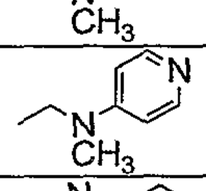
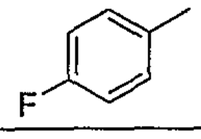
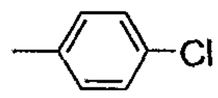
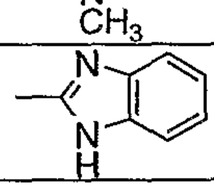
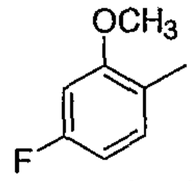
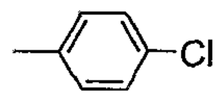
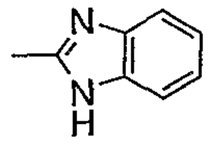
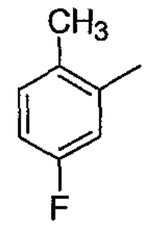
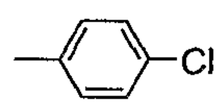
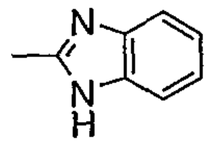
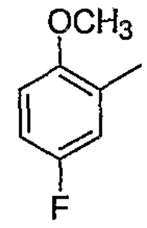
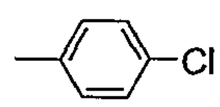
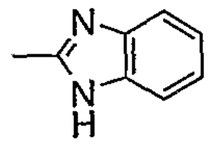
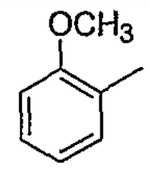
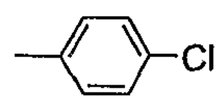
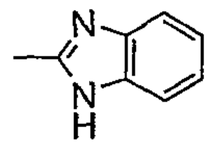
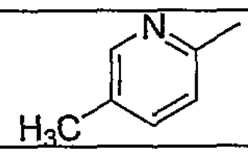
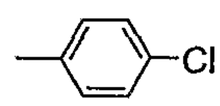
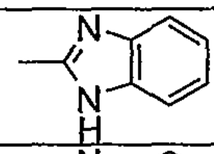
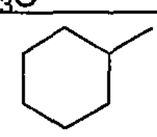
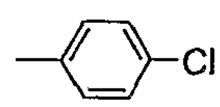
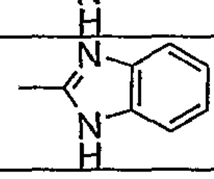
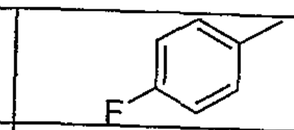
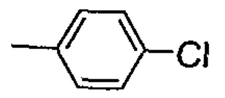
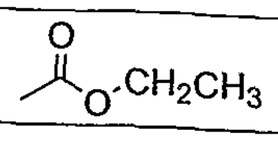
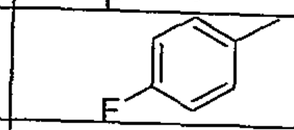
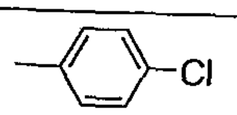
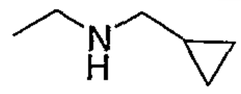
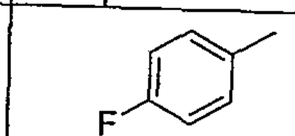
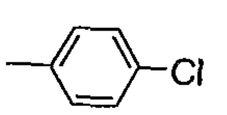
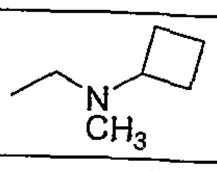
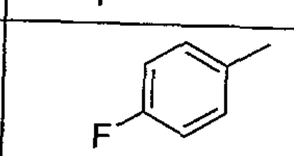
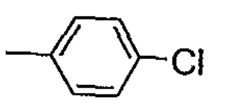
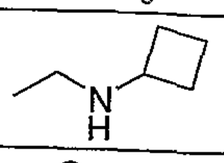
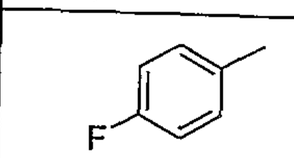
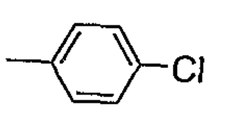
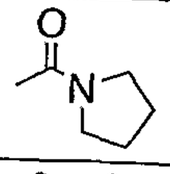
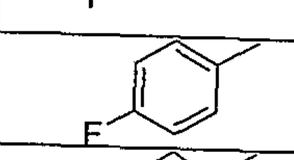
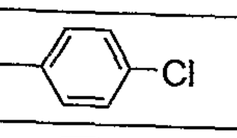
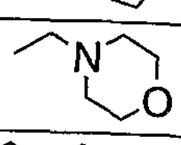
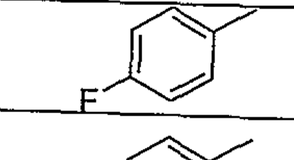
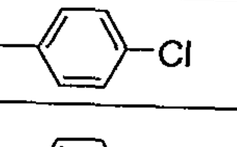
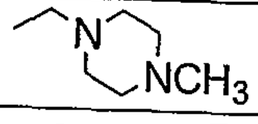
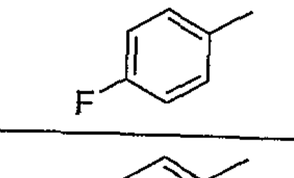
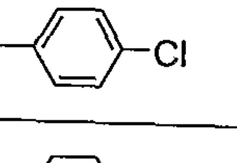
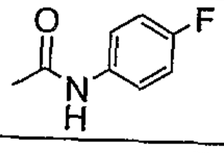
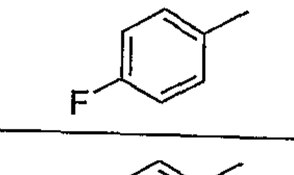
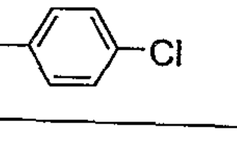
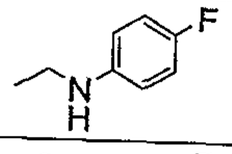
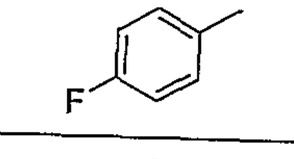
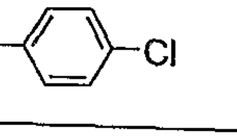
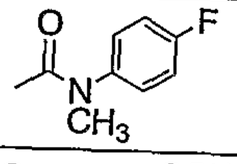
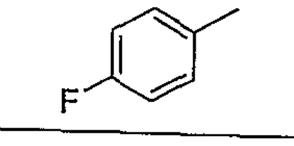
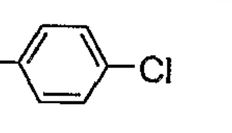
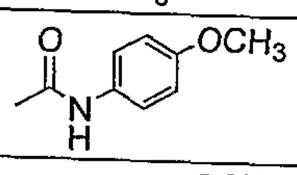
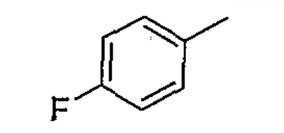
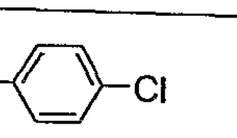
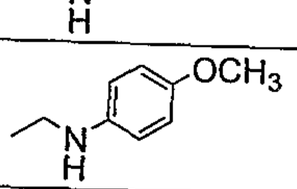
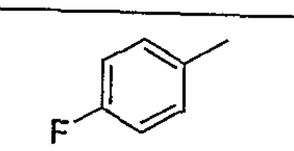
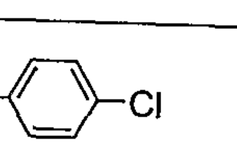
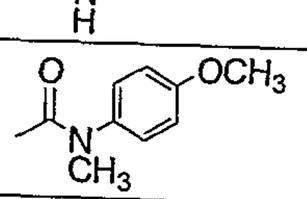
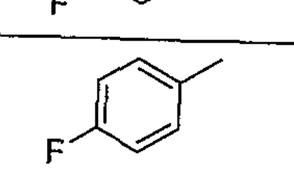
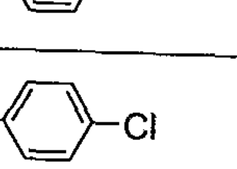
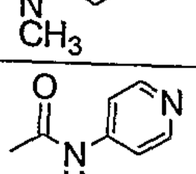
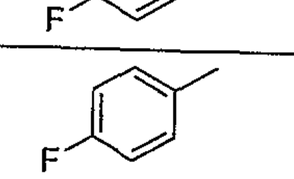
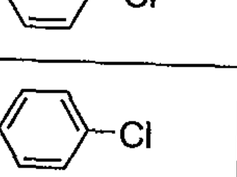
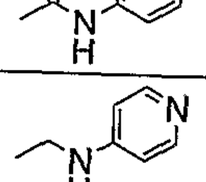
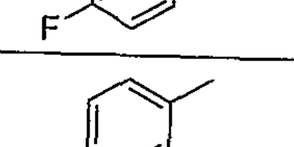
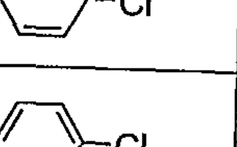
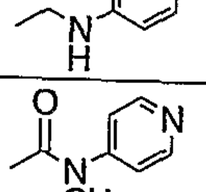
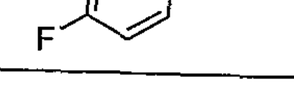
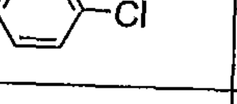
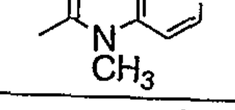
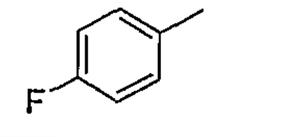
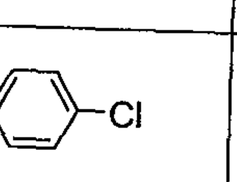
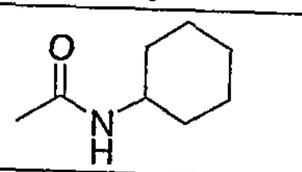
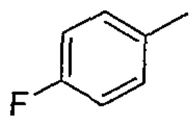
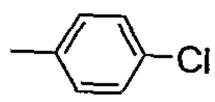
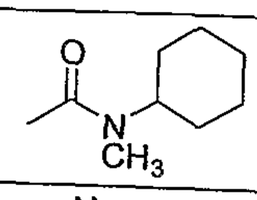
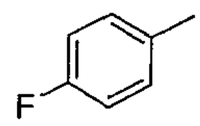
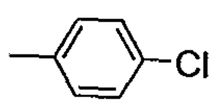
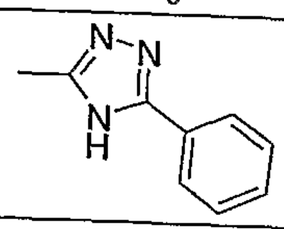
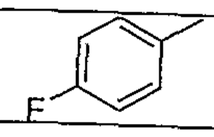
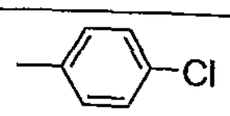
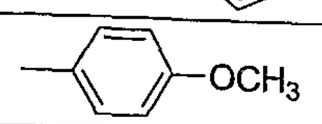
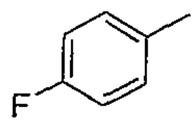
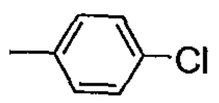
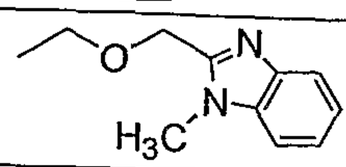
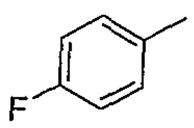
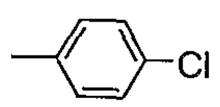
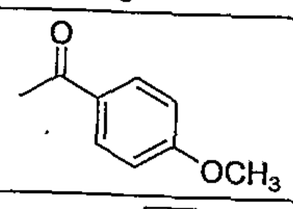
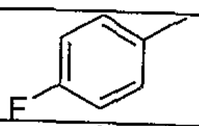
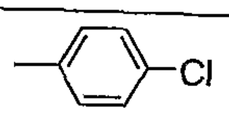
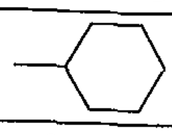
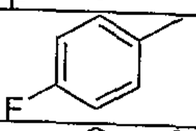
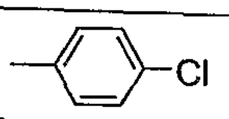
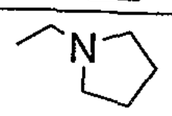
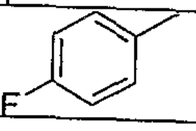
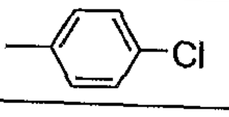
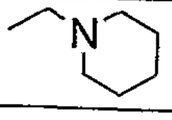
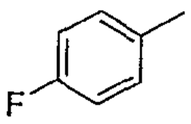
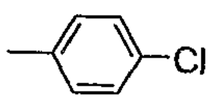
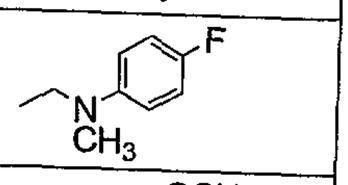
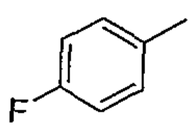
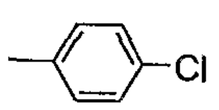
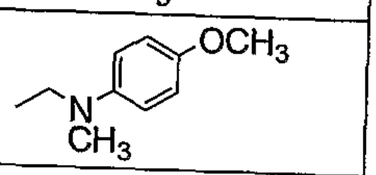
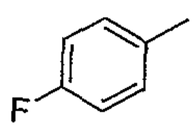
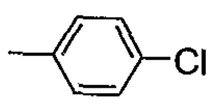
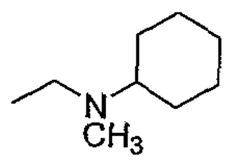
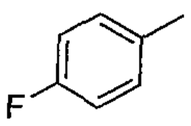
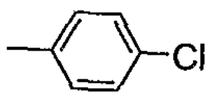
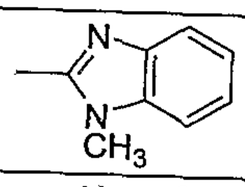
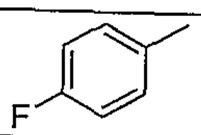
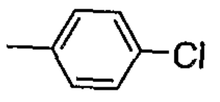
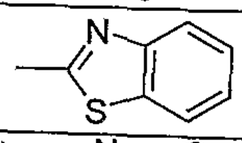
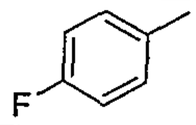
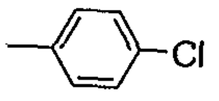
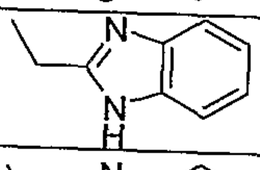
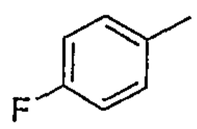
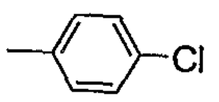
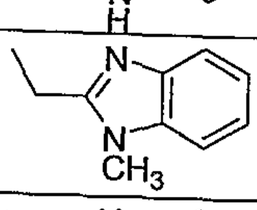
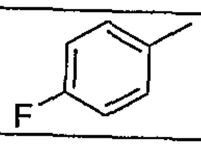
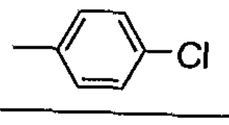
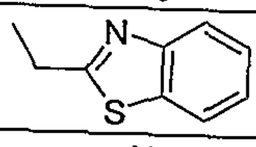
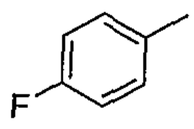
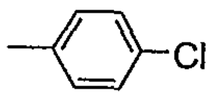
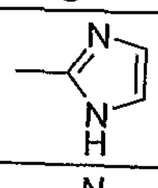
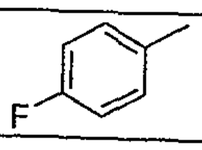
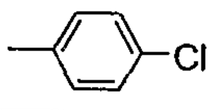
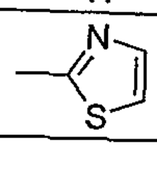
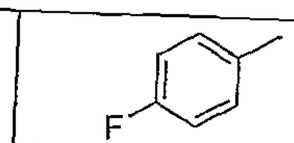
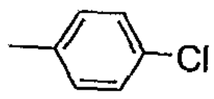
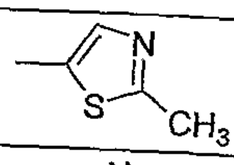
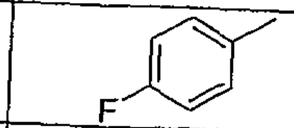
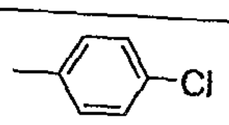
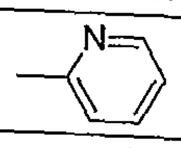
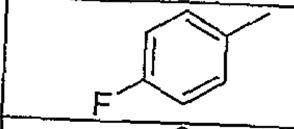
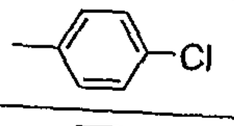
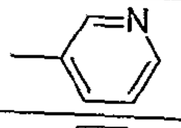
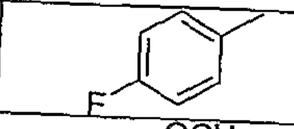
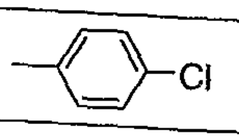
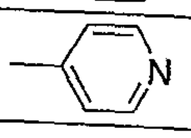
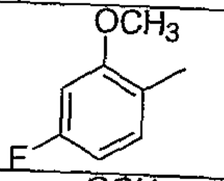
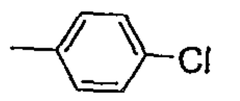
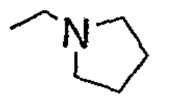
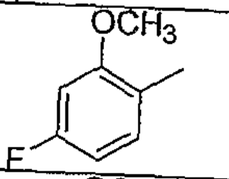
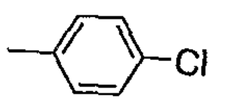
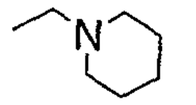
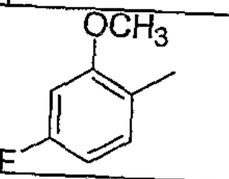
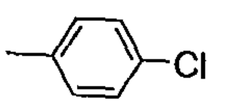
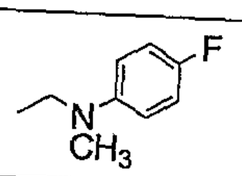
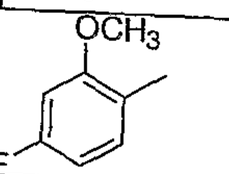
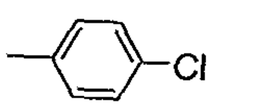
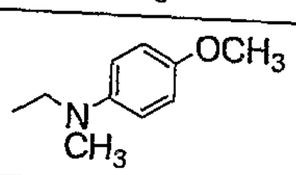
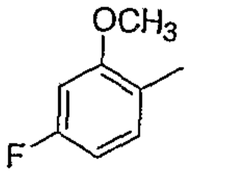
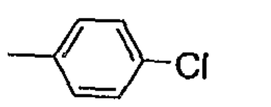
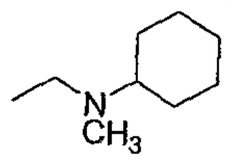
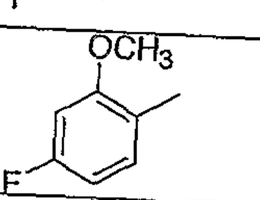
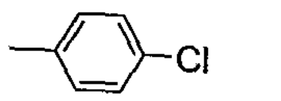
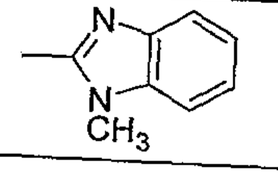
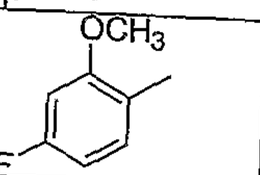
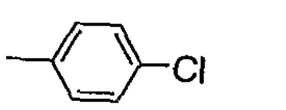
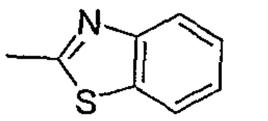
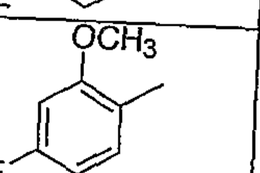
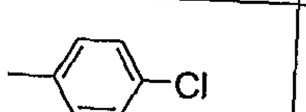
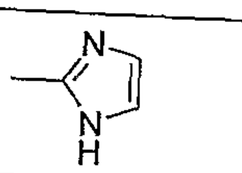
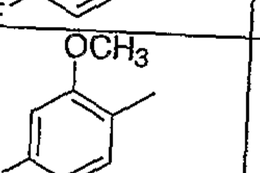
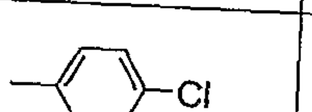
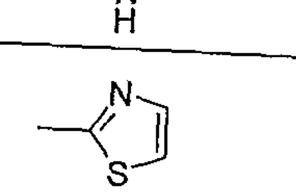
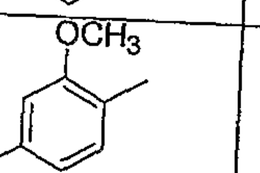
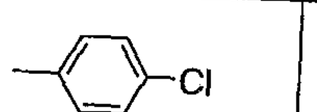
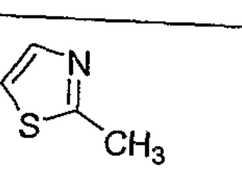
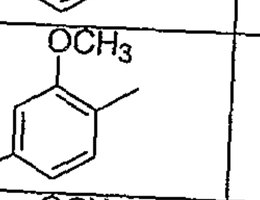
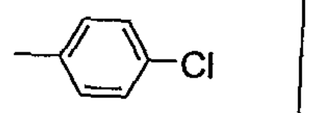
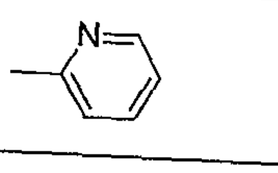
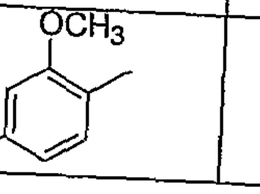
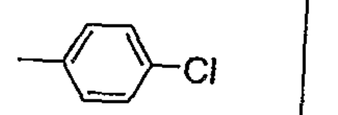
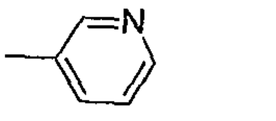
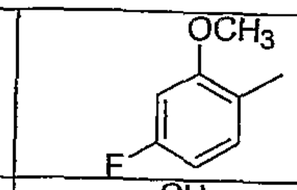
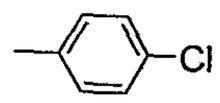
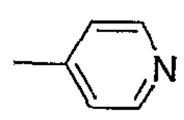
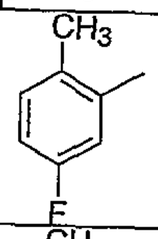
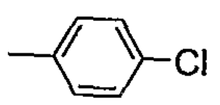
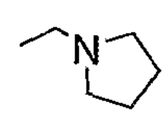
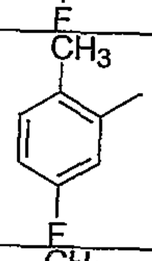
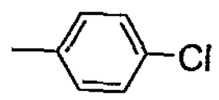
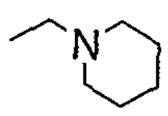
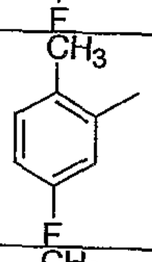
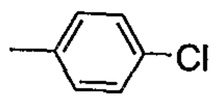
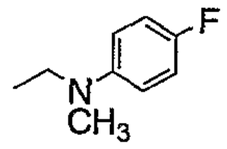
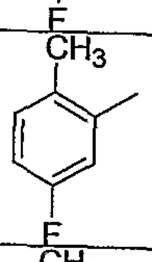
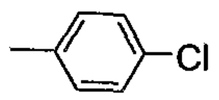
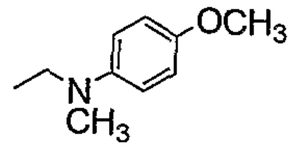
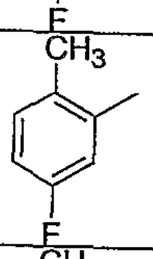
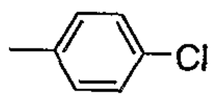
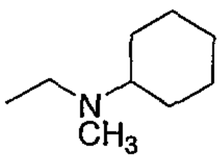
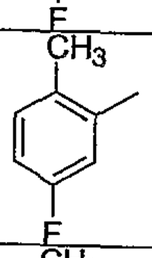
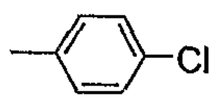
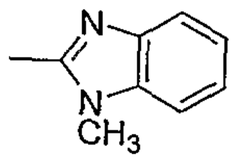
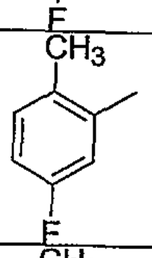
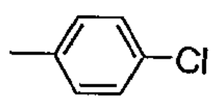
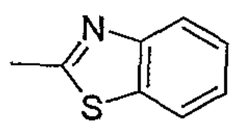
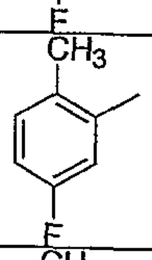
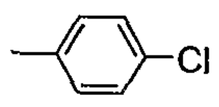
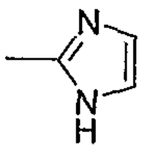
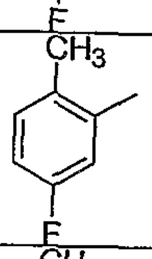
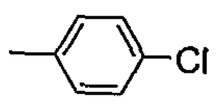
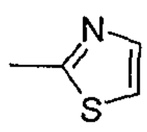
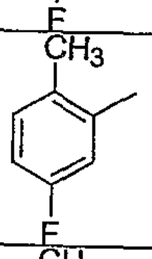
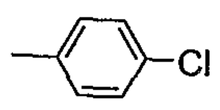
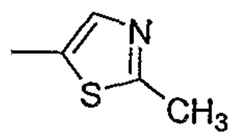
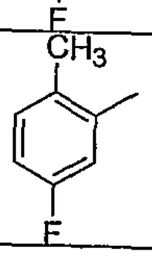
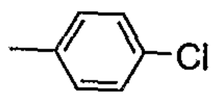
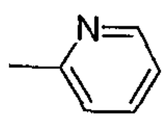
E400			
E401			
E402			
E403			
E404			
E405			

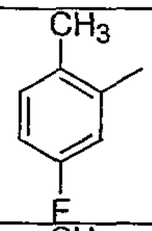
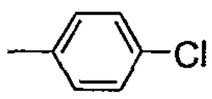
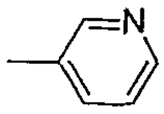
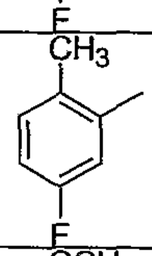
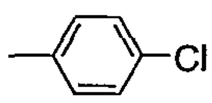
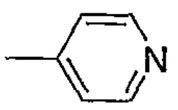
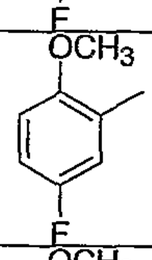
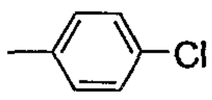
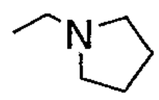
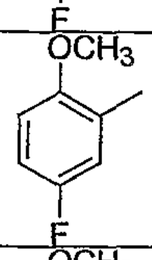
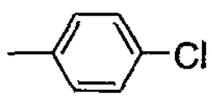
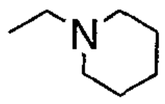
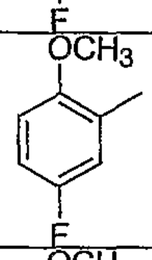
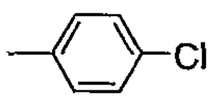
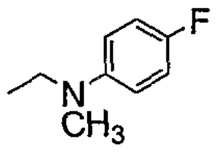
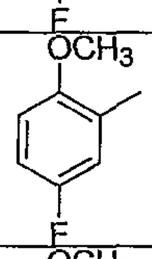
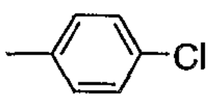
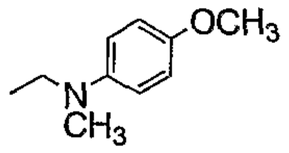
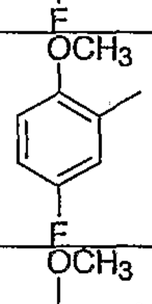
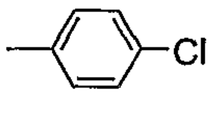
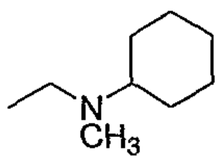
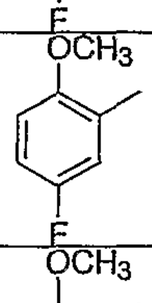
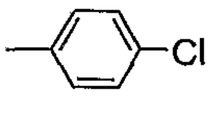
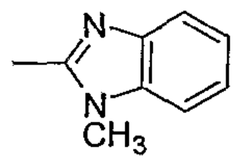
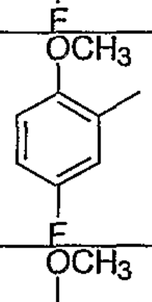
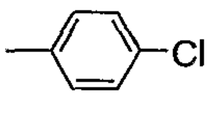
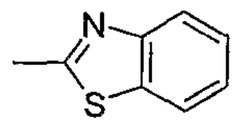
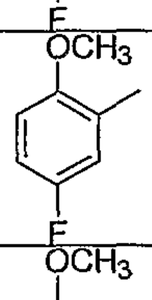
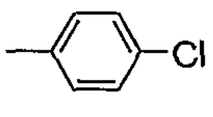
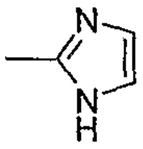
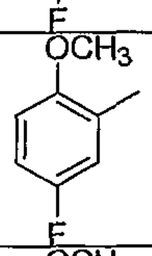
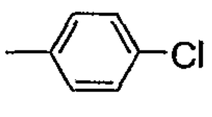
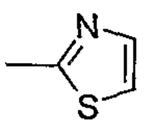
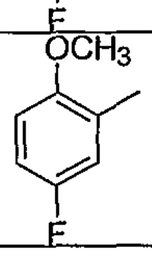
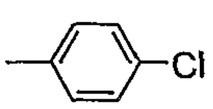
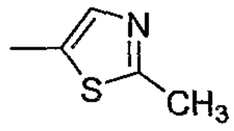
E406			
E407			
E408			
E409			
E410			
E411			
E412			
E413			
E414			
E415			
E416			
E417			
E418			
E419			
E420			

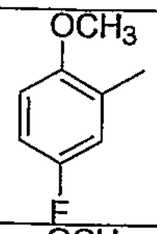
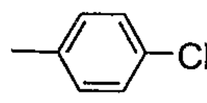
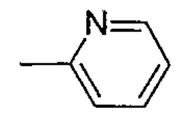
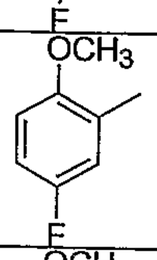
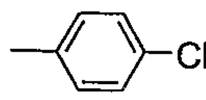
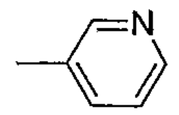
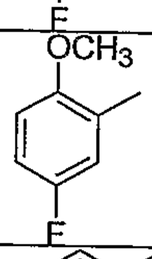
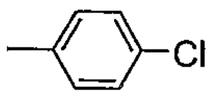
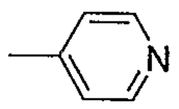
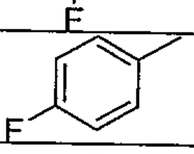
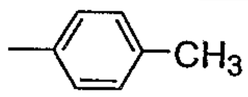
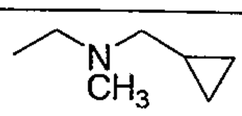
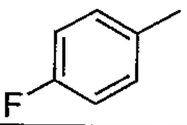
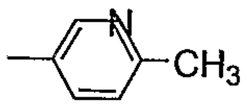
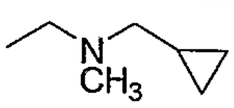
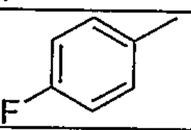
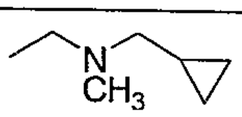
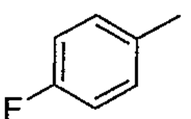
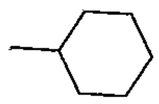
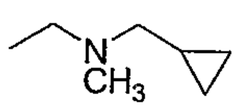
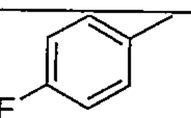
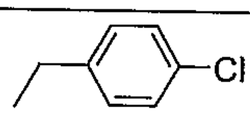
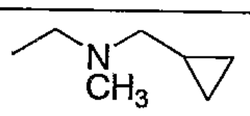
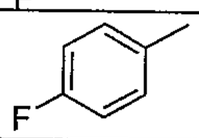
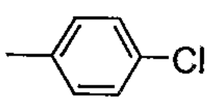
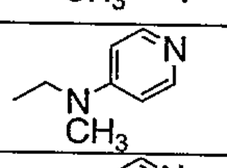
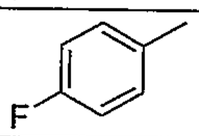
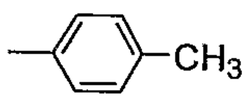
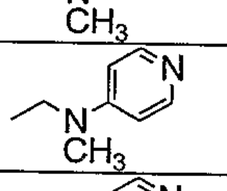
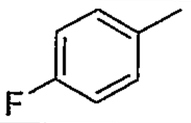
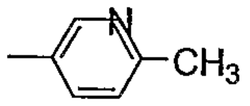
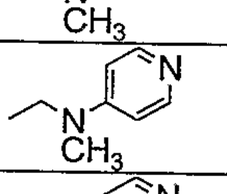
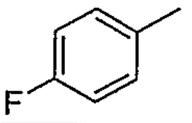
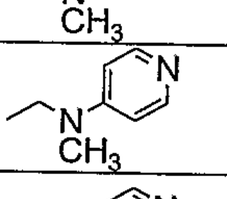
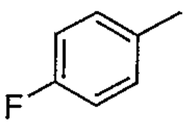
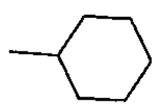
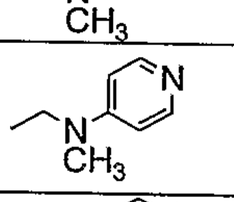
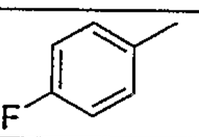
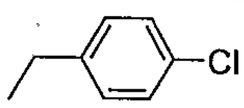
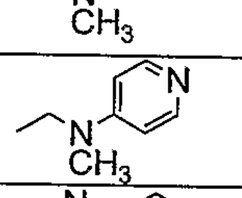
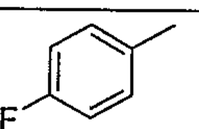
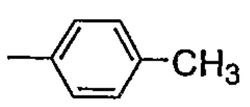
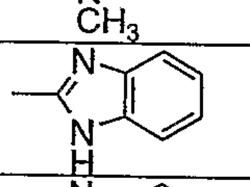
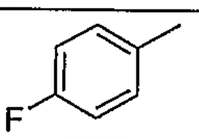
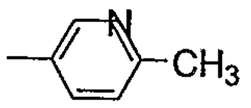
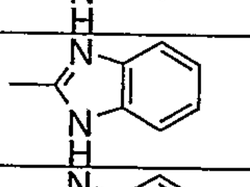
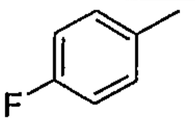
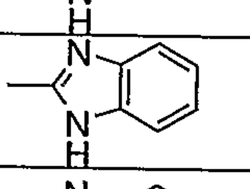
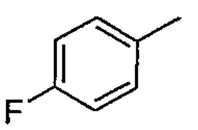
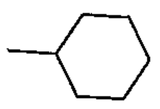
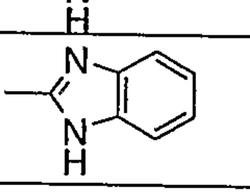
E421			
E422			
E423			
E424			
E425			
E426			
E427			
E428			
E429			
E430			
E431			
E432			
E433			
E434			
E435			
E436			
E437			
E438			

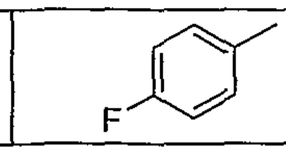
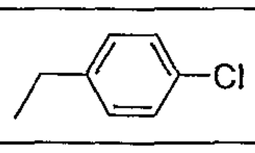
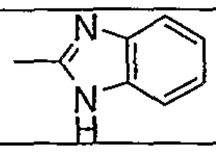
E439			
E440			
E441			
E442			
E443			
E444			
E445			
E446			
E447			
E448			
E449			
E450			
E451			
E452			
E453			
E454			
E455			
E456			

E457			
E458			
E459			
E460			
E461			
E462			
E463			
E464			
E465			
E466			
E467			
E468			
E469			
E470			
E471			
E472			

E473			
E474			
E475			
E476			
E477			
E478			
E479			
E480			
E481			
E482			
E483			
E484			

E485			
E486			
E487			
E488			
E489			
E490			
E491			
E492			
E493			
E494			
E495			
E496			

E497			
E498			
E499			
E500			
E501			
E502		CH_3	
E503			
E504			
E505			
E506			
E507			
E508		CH_3	
E509			
E510			
E511			
E512			
E513		CH_3	
E514			

E515			

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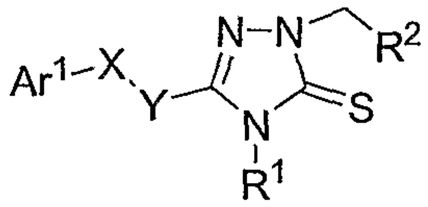
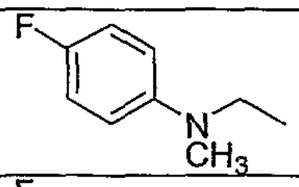
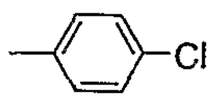
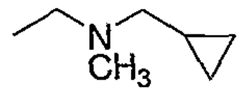
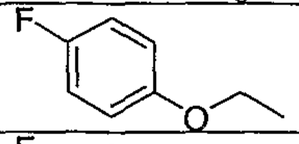
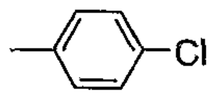
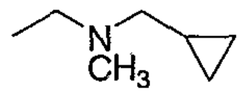
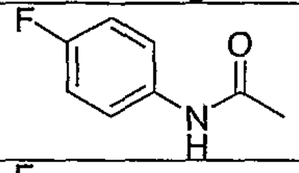
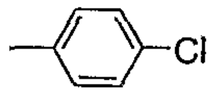
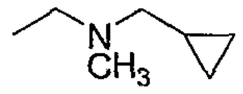
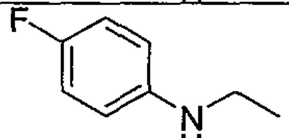
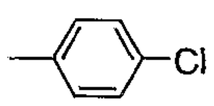
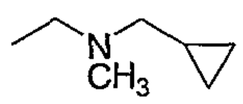
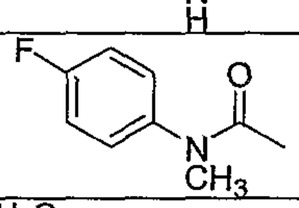
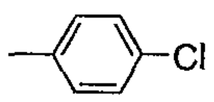
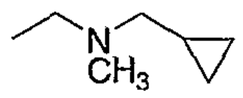
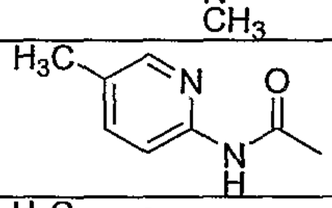
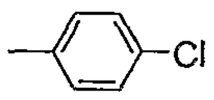
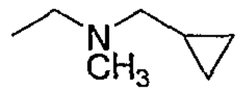
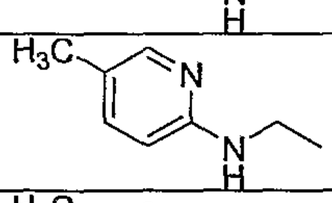
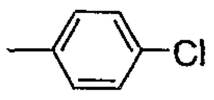
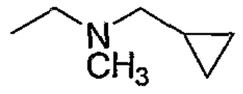
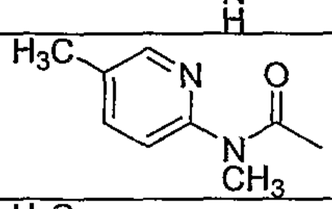
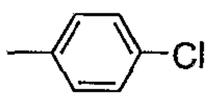
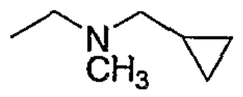
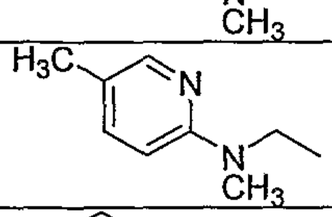
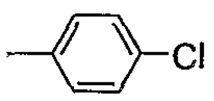
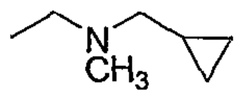
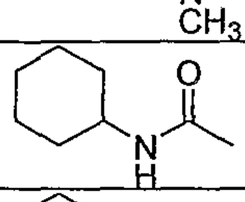
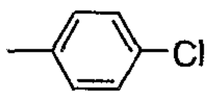
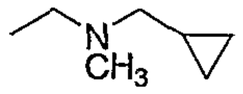
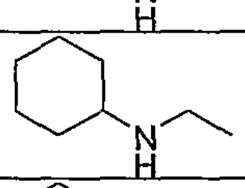
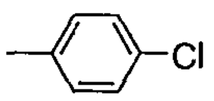
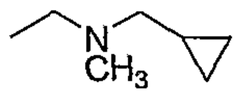
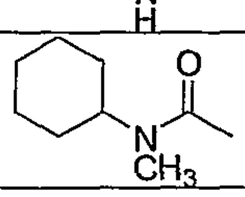
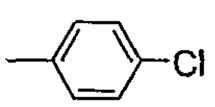
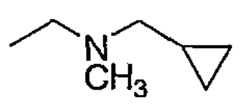
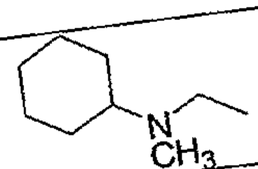
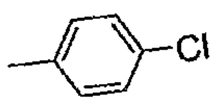
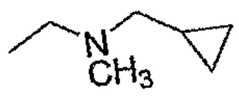
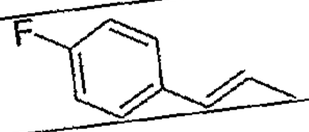
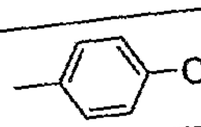
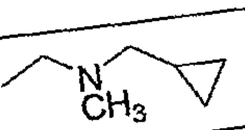
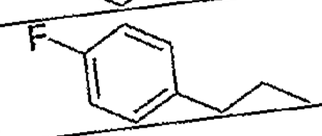
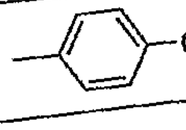
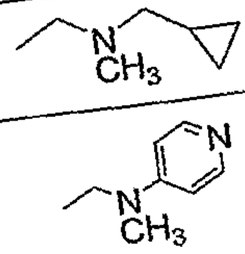
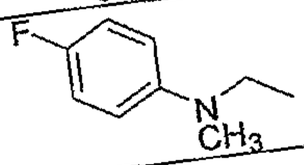
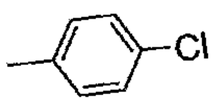
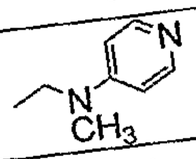
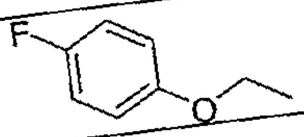
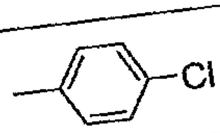
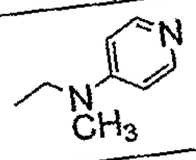
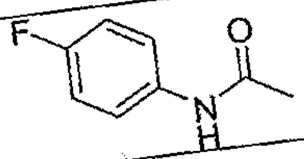
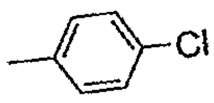
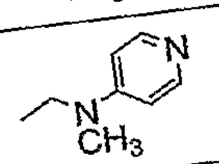
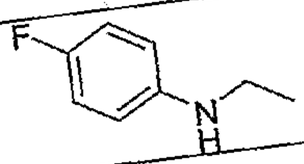
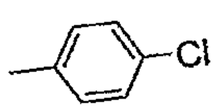
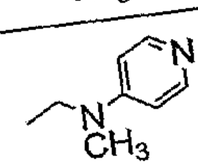
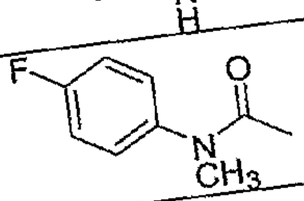
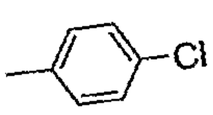
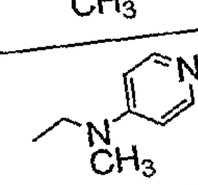
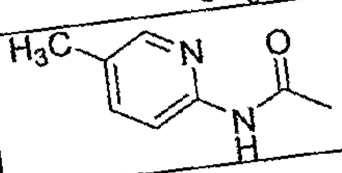
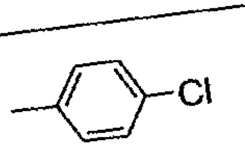
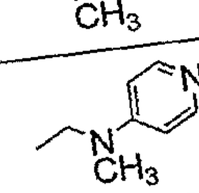
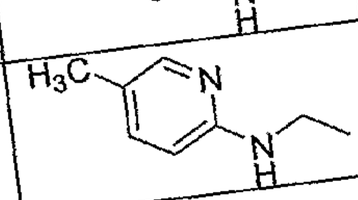
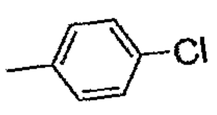
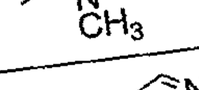
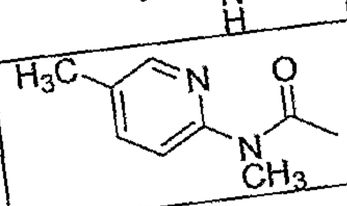
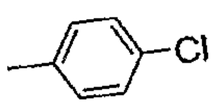
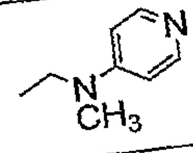
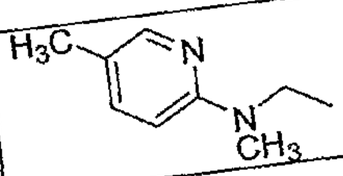
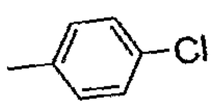
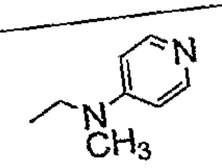
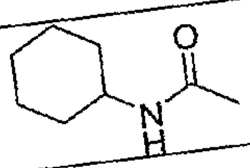
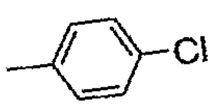
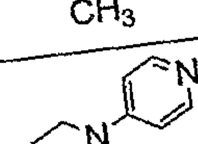
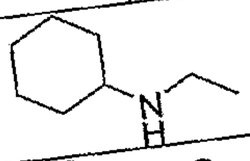
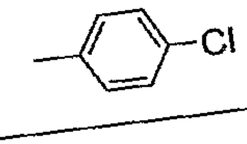
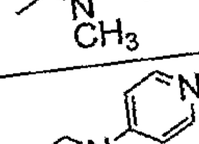
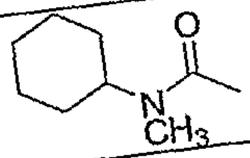
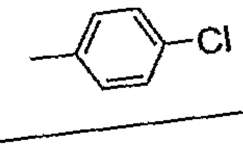
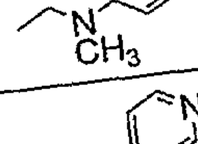
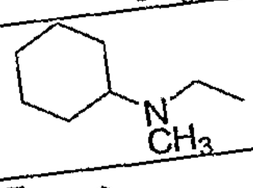
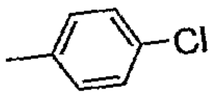
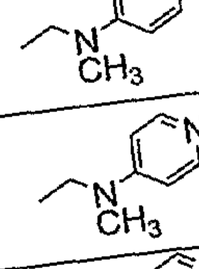
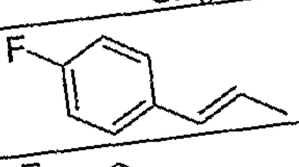
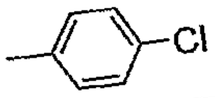
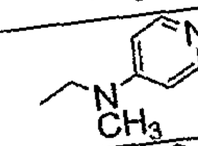
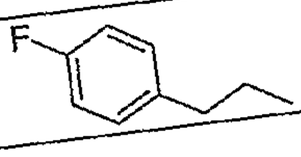
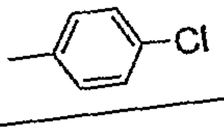
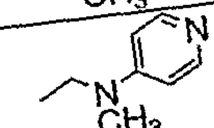
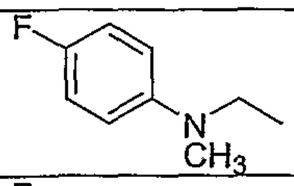
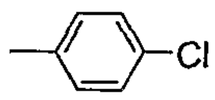
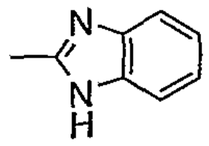
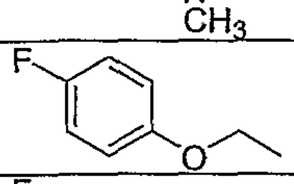
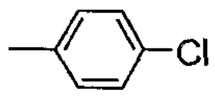
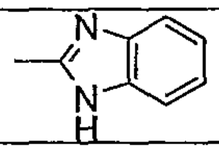
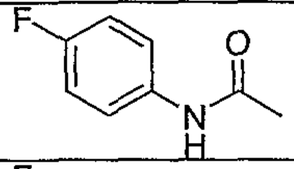
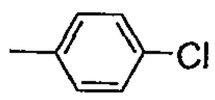
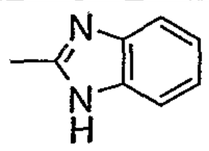
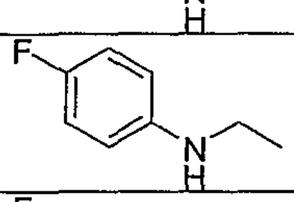
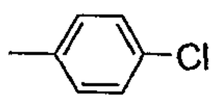
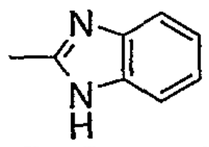
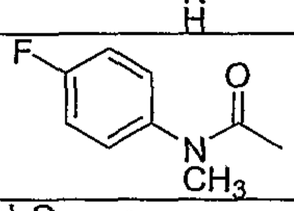
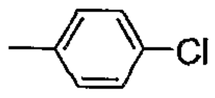
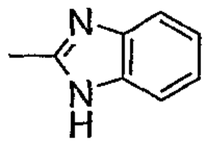
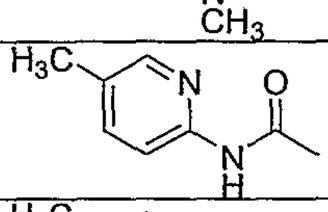
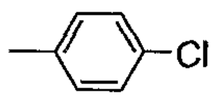
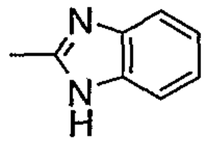
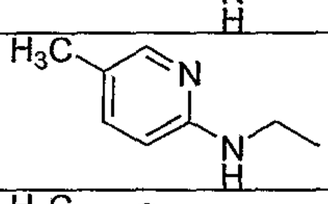
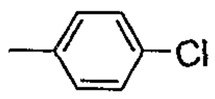
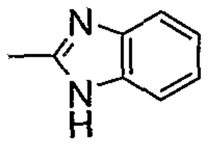
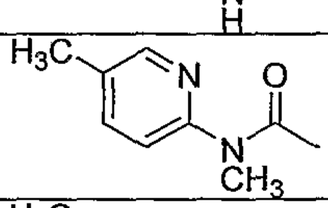
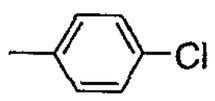
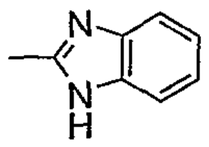
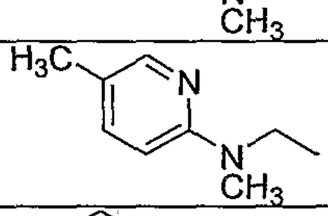
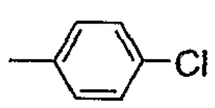
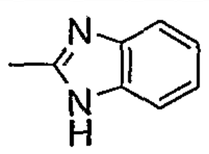
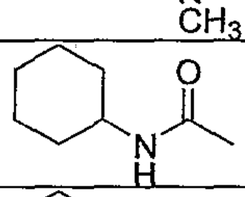
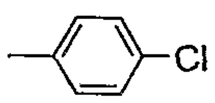
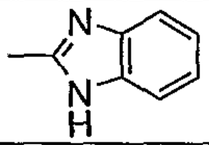
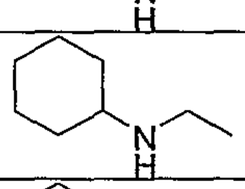
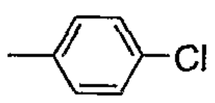
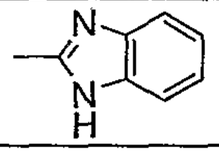
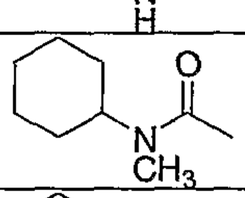
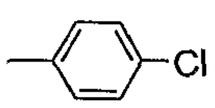
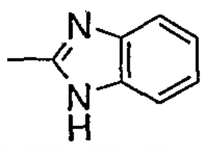
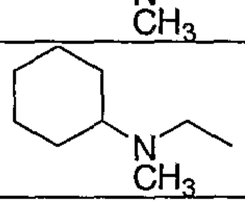
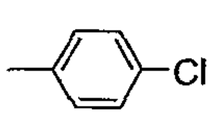
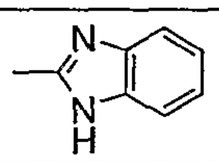
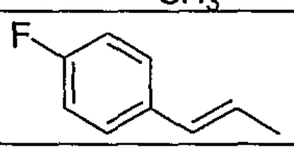
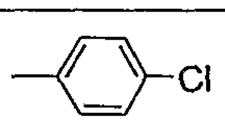
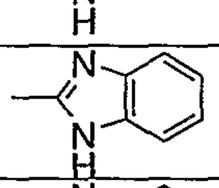
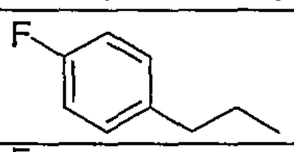
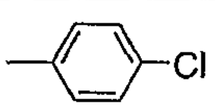
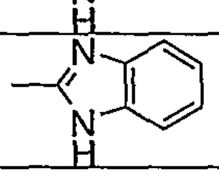
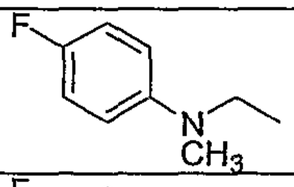
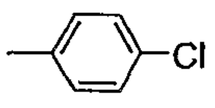
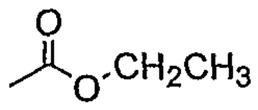
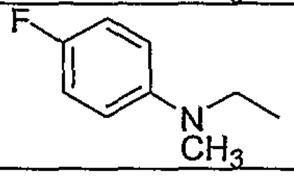
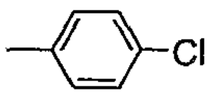
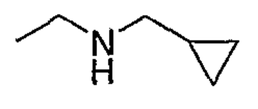
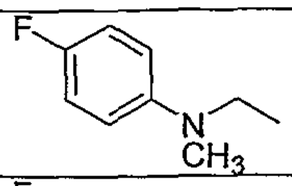
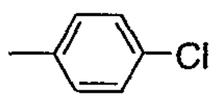
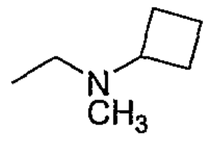
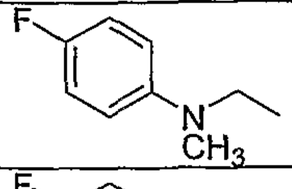
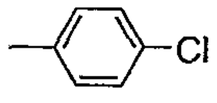
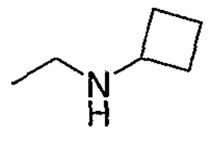
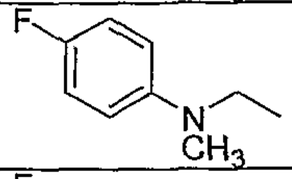
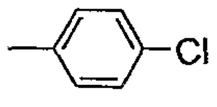
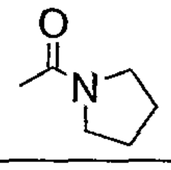
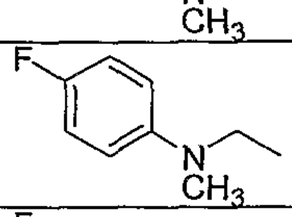
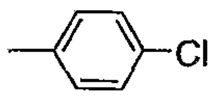
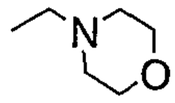
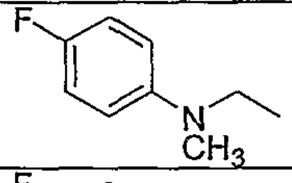
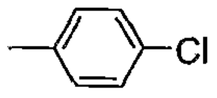
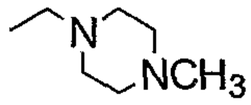
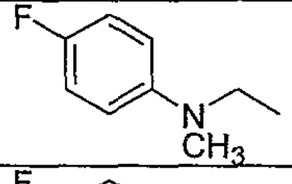
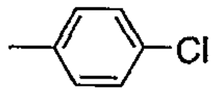
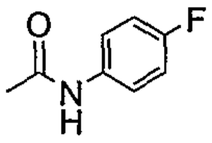
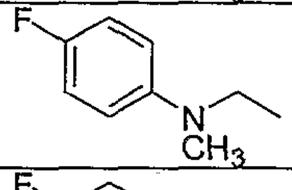
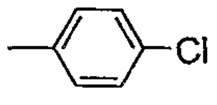
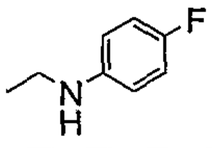
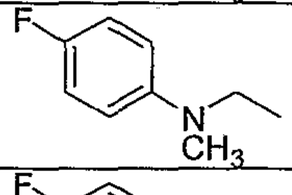
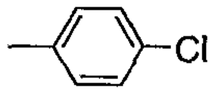
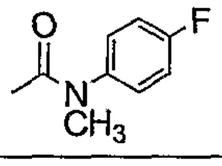
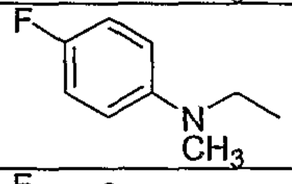
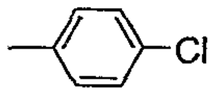
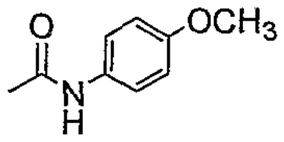
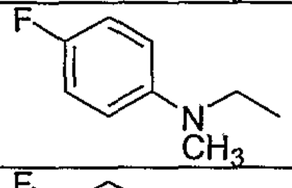
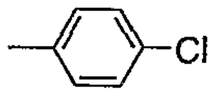
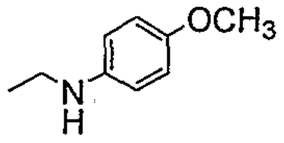
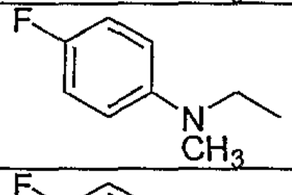
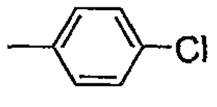
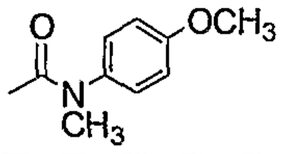
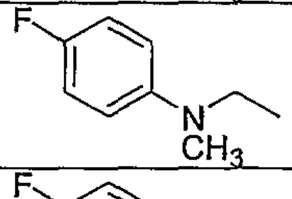
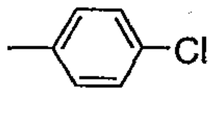
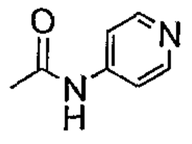
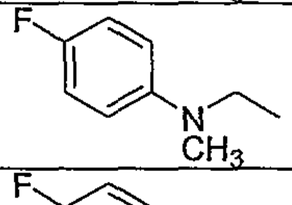
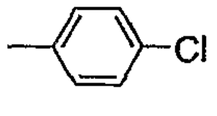
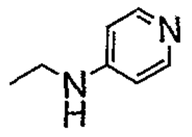
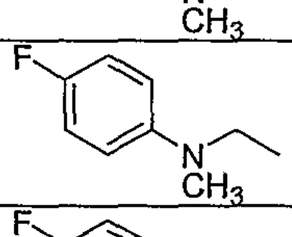
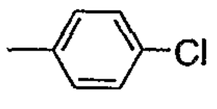
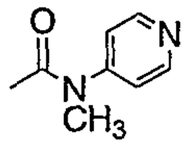
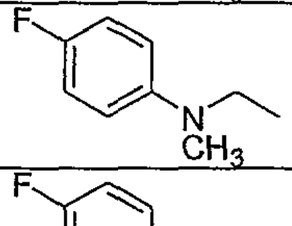
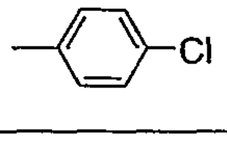
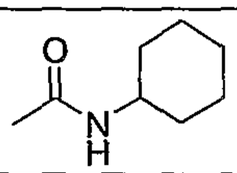
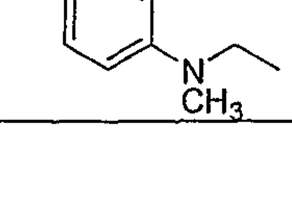
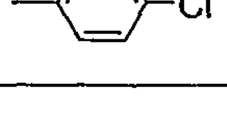
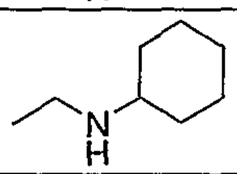
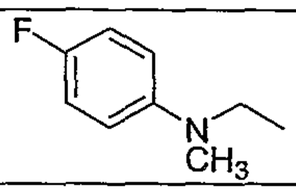
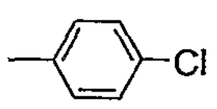
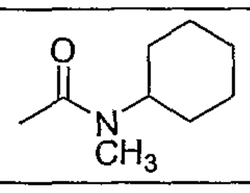
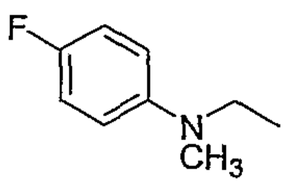
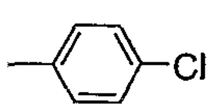
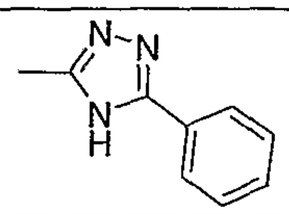
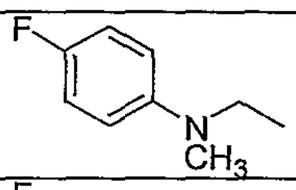
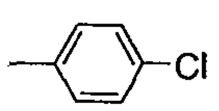
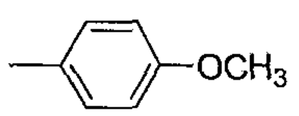
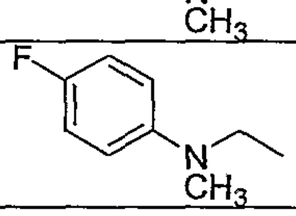
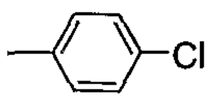
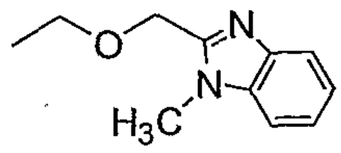
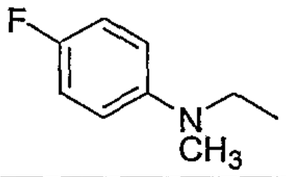
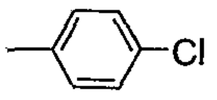
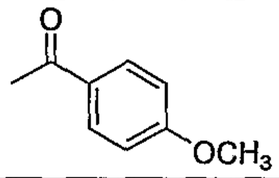
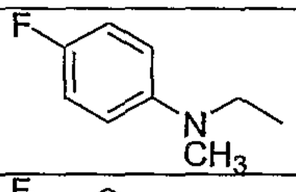
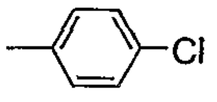
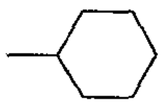
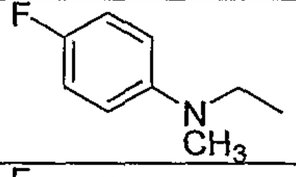
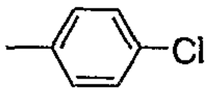
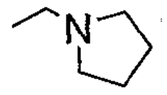
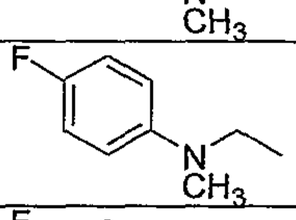
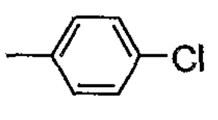
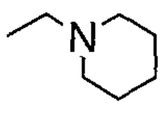
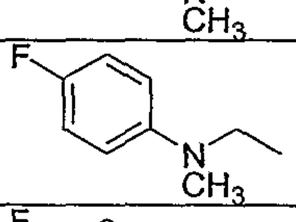
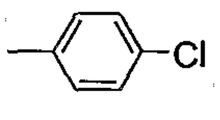
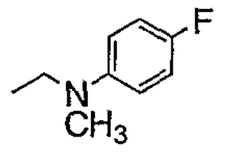
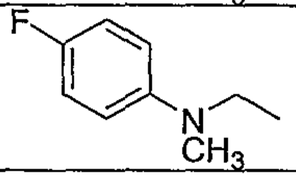
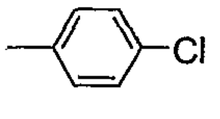
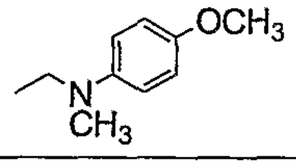
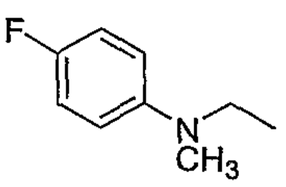
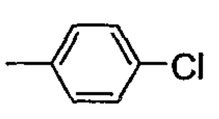
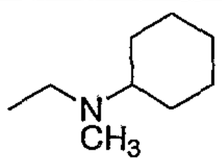
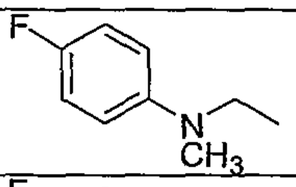
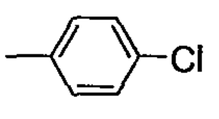
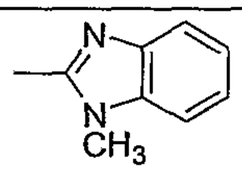
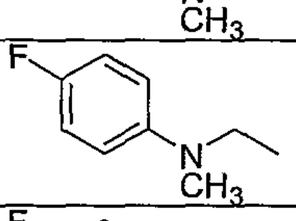
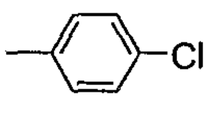
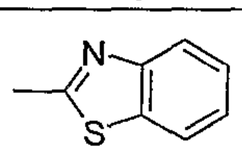
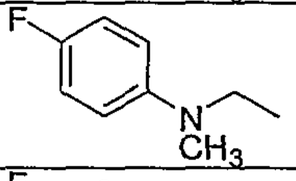
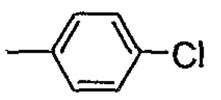
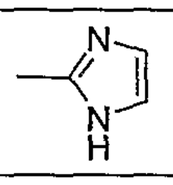
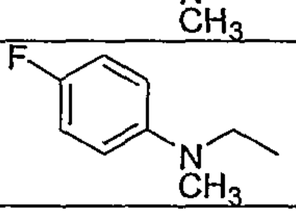
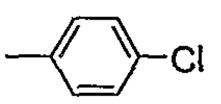
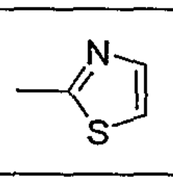


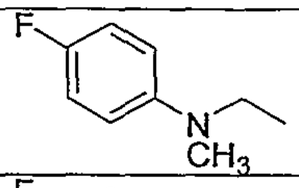
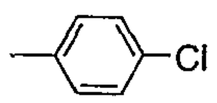
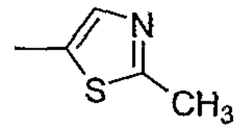
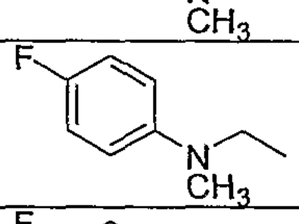
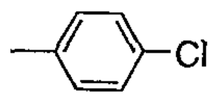
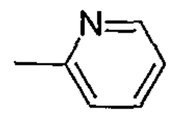
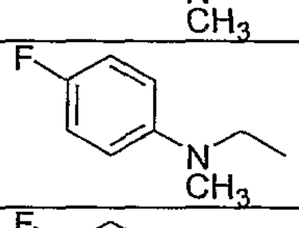
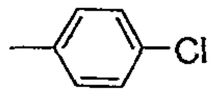
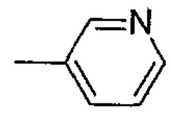
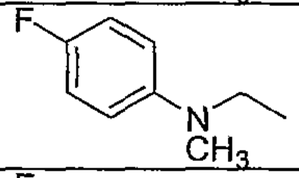
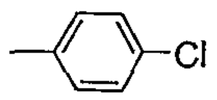
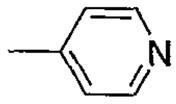
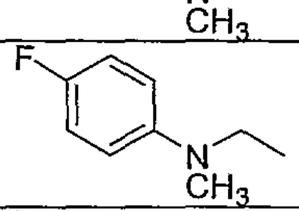
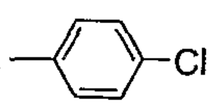
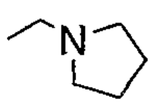
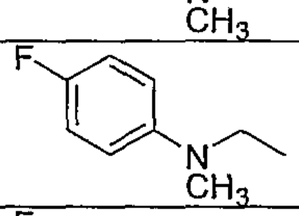
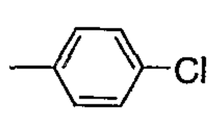
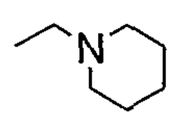
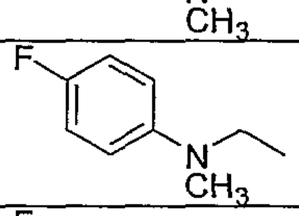
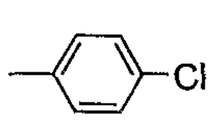
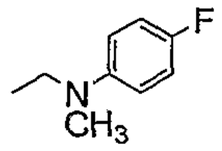
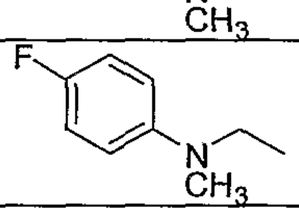
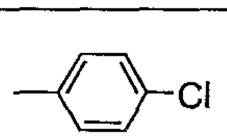
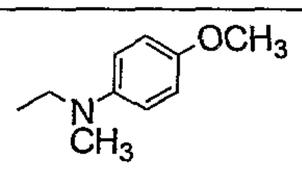
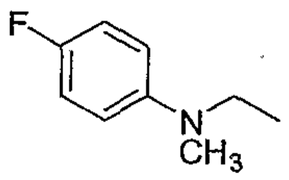
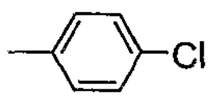
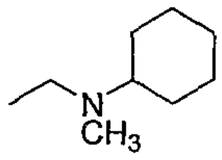
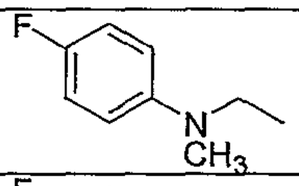
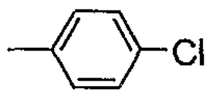
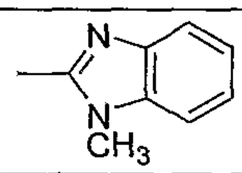
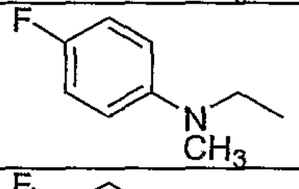
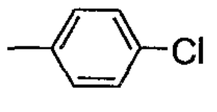
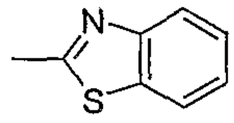
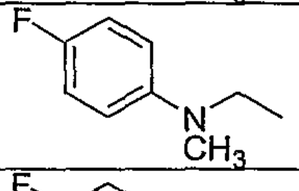
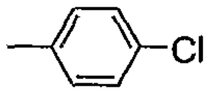
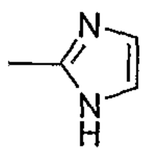
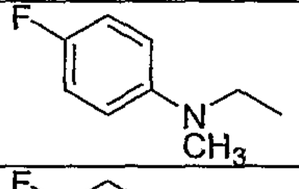
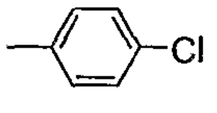
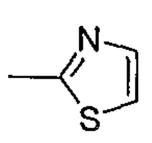
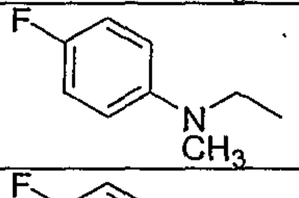
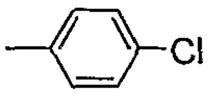
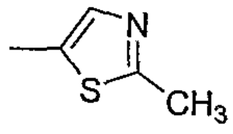
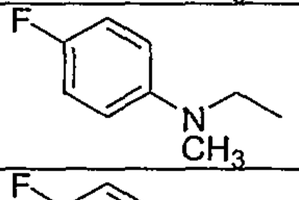
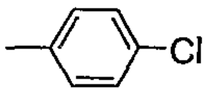
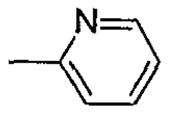
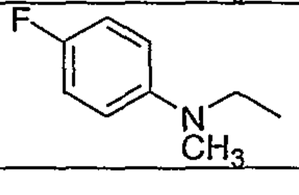
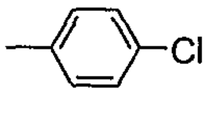
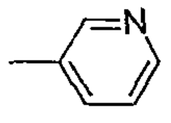
Cpd. No.	Ar^1-X-Y	R^1	R^2
E516			
E517			
E518			
E519			
E520			
E521			
E522			
E523			
E524			
E525			
E526			
E527			

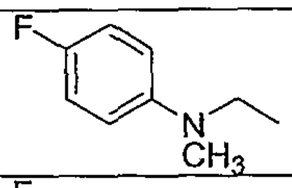
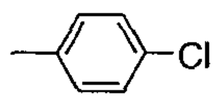
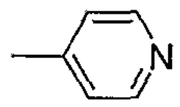
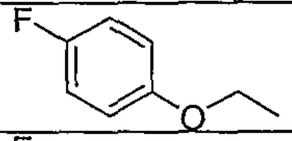
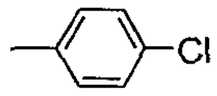
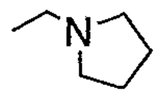
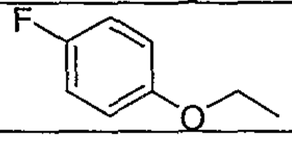
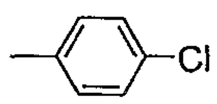
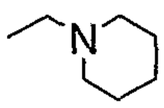
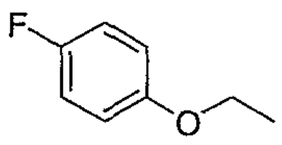
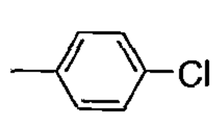
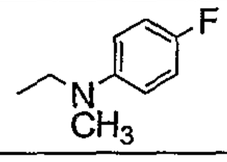
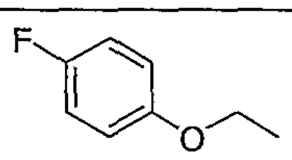
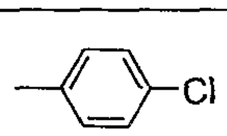
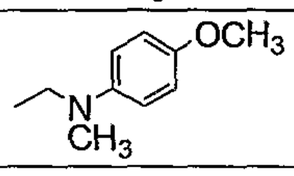
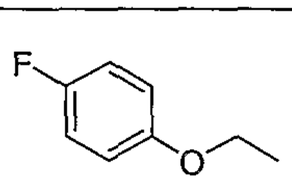
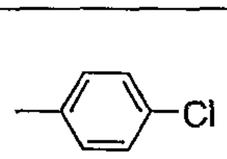
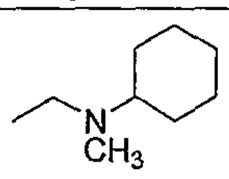
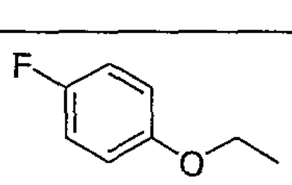
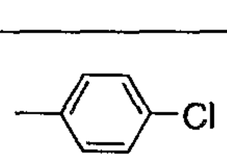
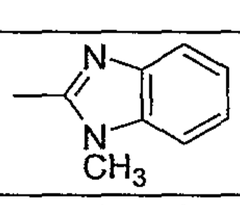
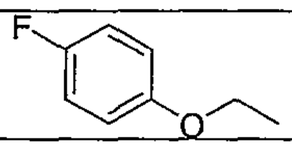
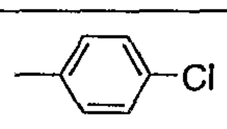
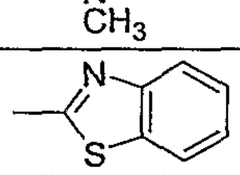
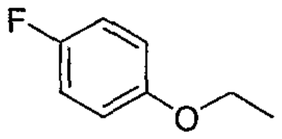
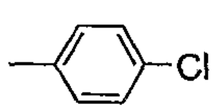
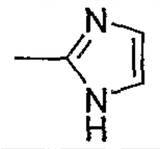
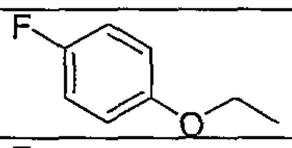
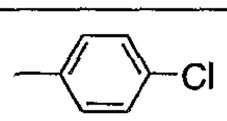
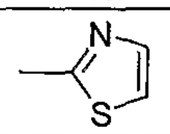
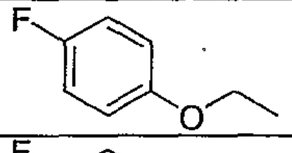
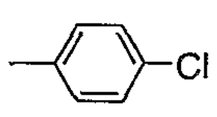
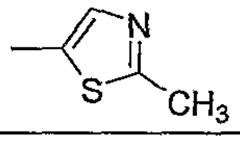
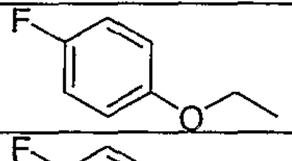
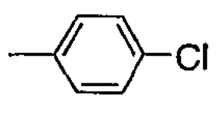
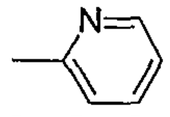
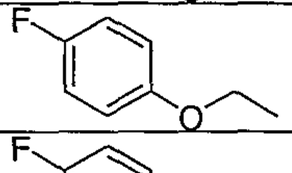
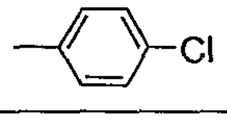
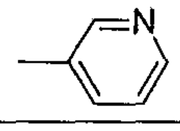
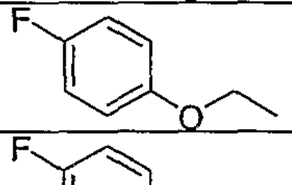
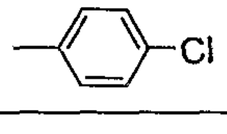
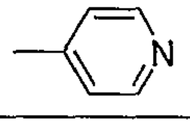
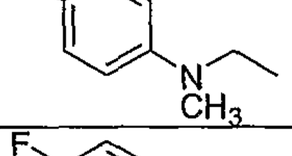
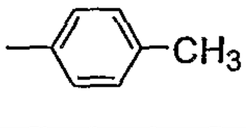
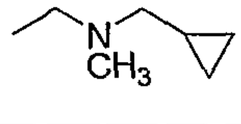
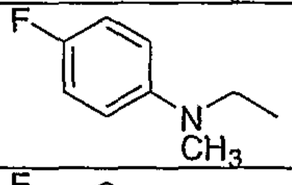
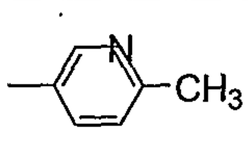
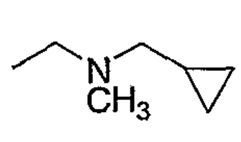
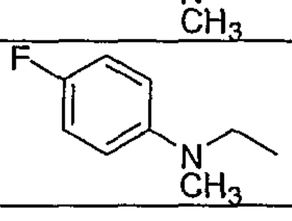
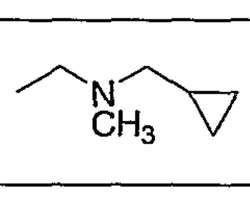
E528			
E529			
E530			
E531			
E532			
E533			
E534			
E535			
E536			
E537			
E538			
E539			
E540			
E541			
E542			
E543			
E544			
E545			

E546			
E547			
E548			
E549			
E550			
E551			
E552			
E553			
E554			
E555			
E556			
E557			
E558			
E559			
E560			
E561			
E562			

E563			
E564			
E565			
E566			
E567			
E568			
E569			
E570			
E571			
E572			
E573			
E574			
E575			
E576			
E577			
E578			

E579			
E580			
E581			
E582			
E583			
E584			
E585			
E586			
E587			
E588			
E589			
E590			
E591			
E592			
E593			

E594			
E595			
E596			
E597			
E598			
E599			
E600			
E601			
E602			
E603			
E604			
E605			
E606			
E607			
E608			
E609			

E610			
E611			
E612			
E613			
E614			
E615			
E616			
E617			
E618			
E619			
E620			
E621			
E622			
E623			
E624			
E625			
E626		CH_3	

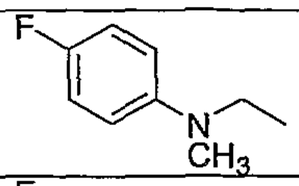
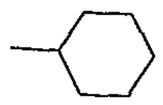
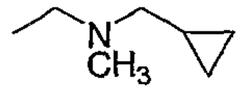
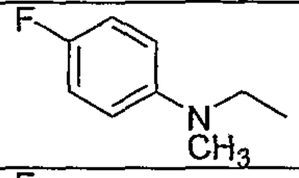
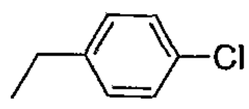
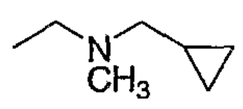
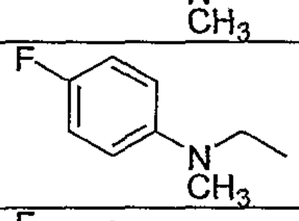
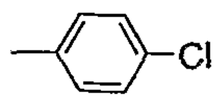
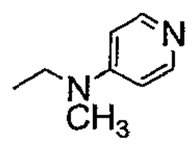
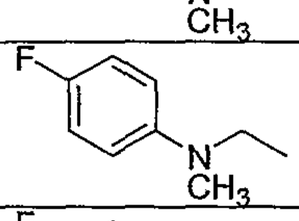
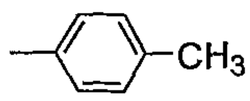
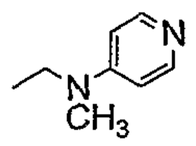
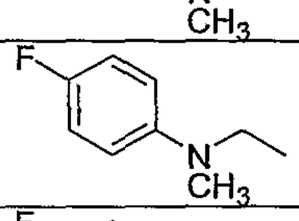
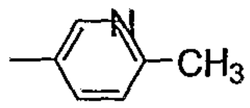
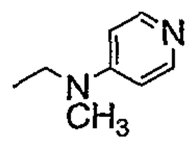
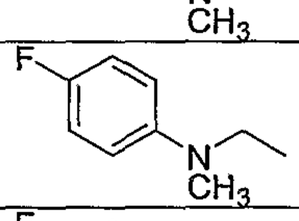
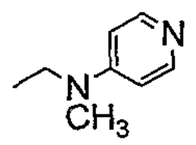
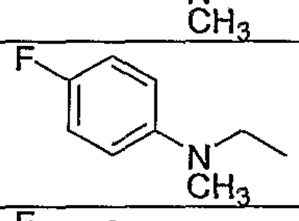
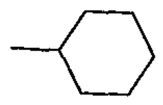
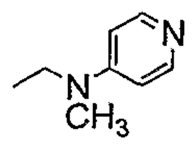
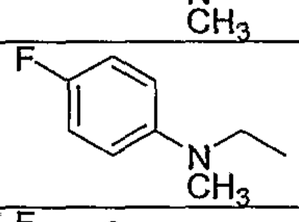
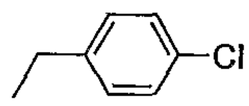
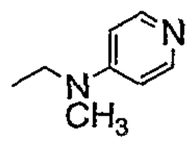
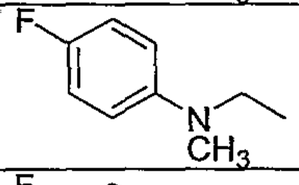
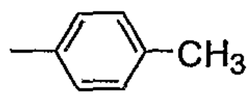
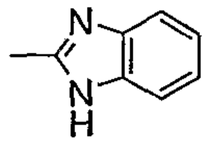
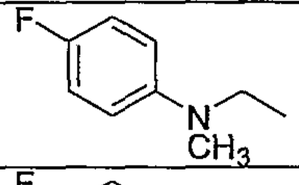
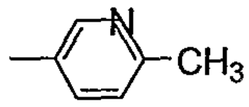
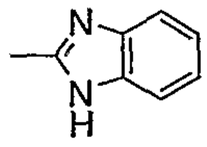
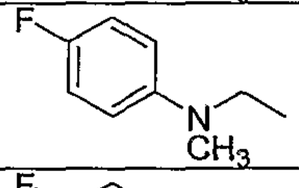
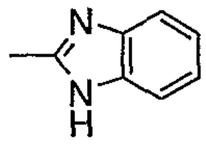
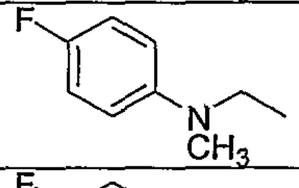
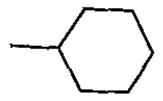
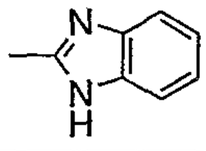
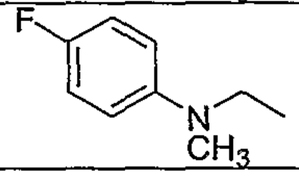
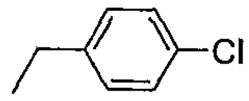
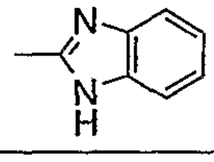
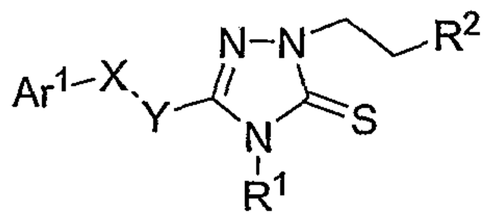
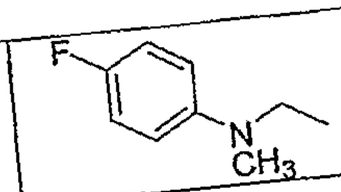
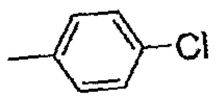
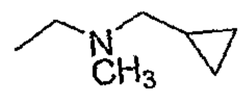
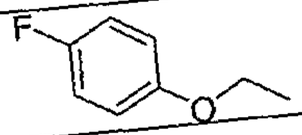
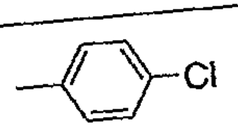
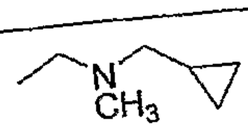
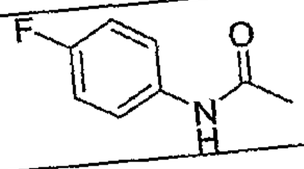
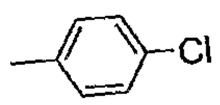
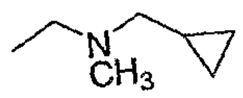
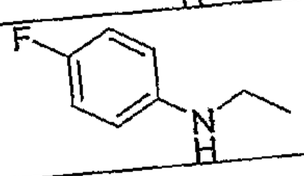
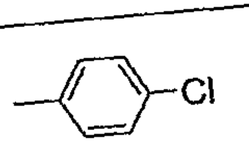
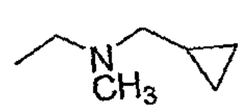
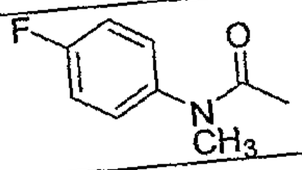
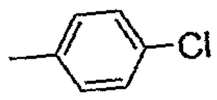
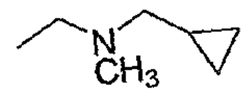
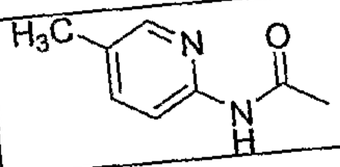
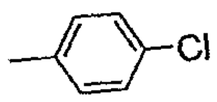
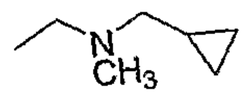
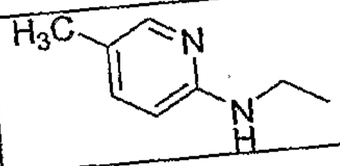
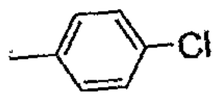
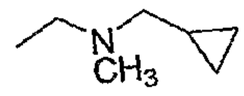
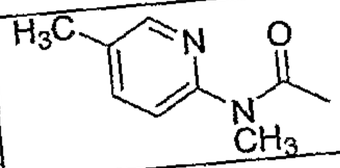
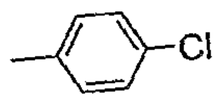
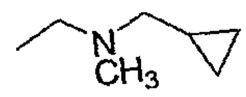
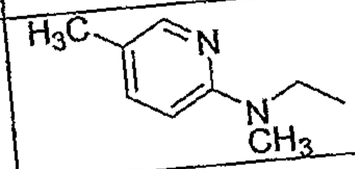
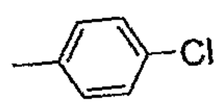
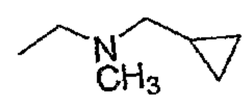
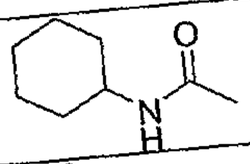
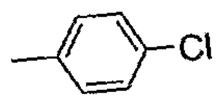
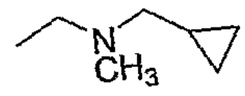
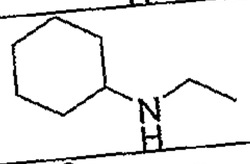
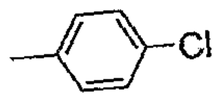
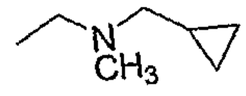
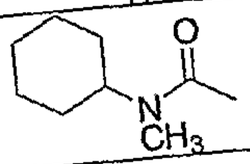
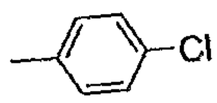
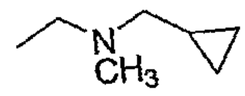
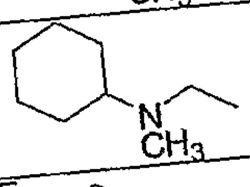
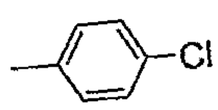
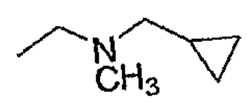
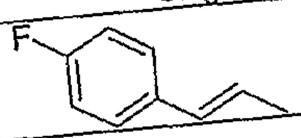
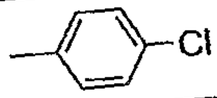
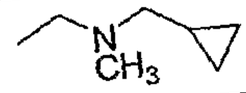
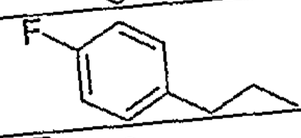
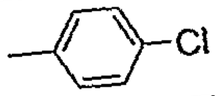
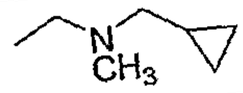
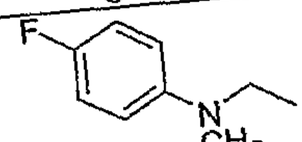
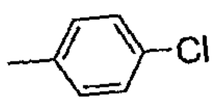
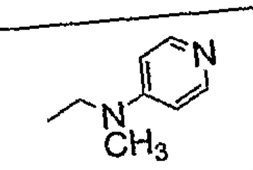
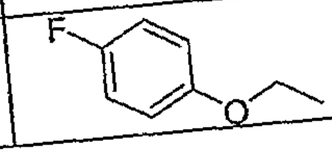
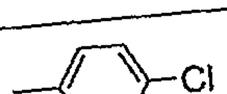
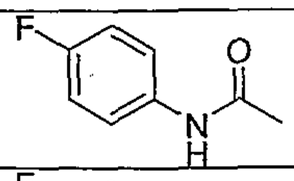
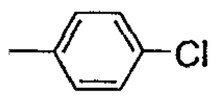
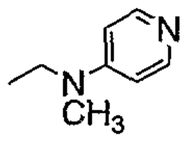
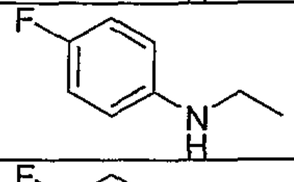
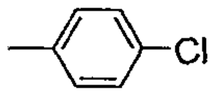
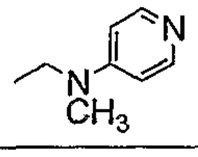
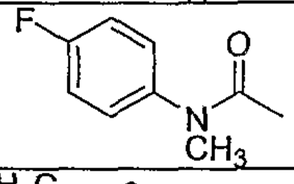
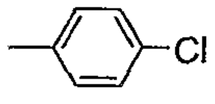
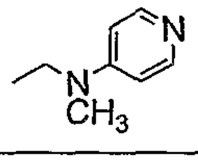
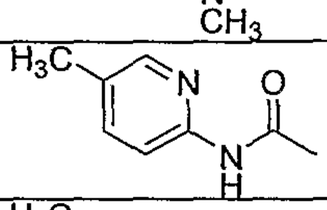
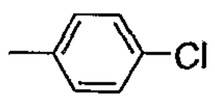
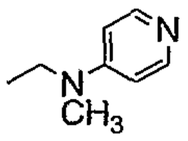
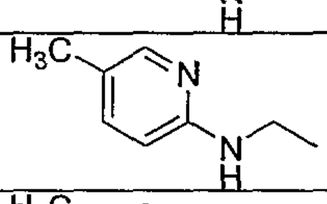
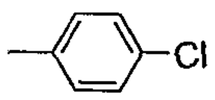
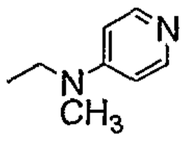
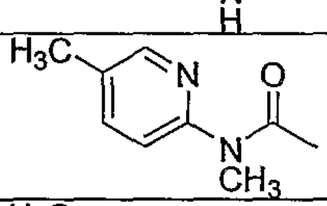
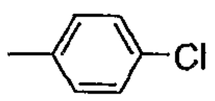
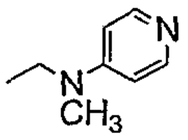
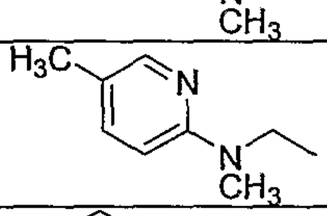
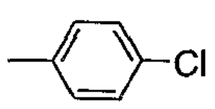
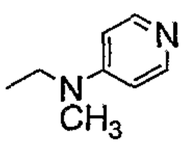
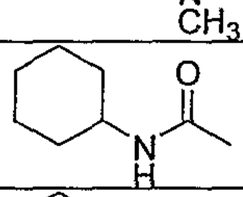
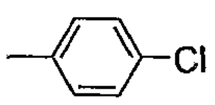
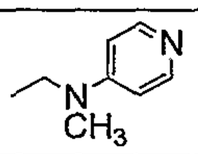
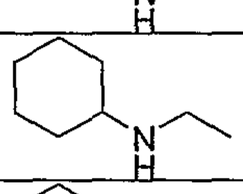
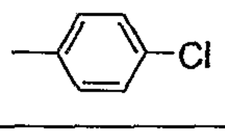
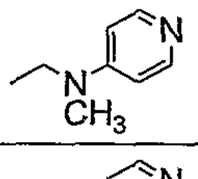
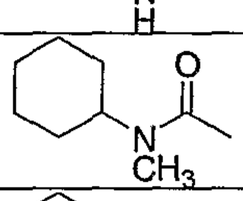
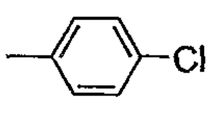
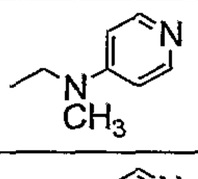
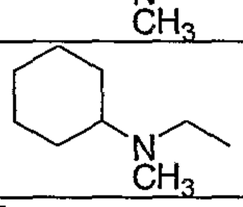
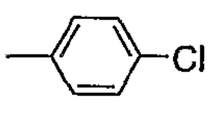
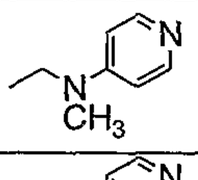
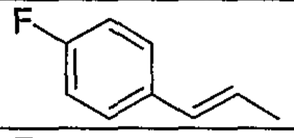
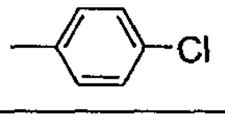
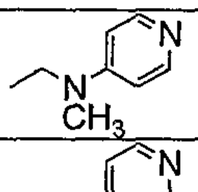
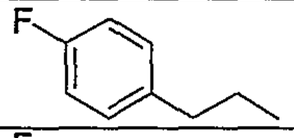
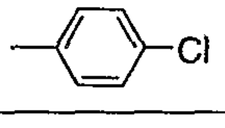
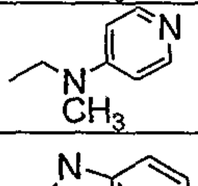
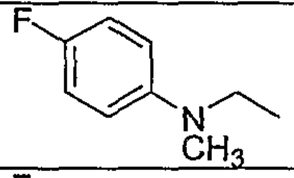
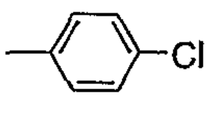
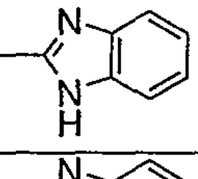
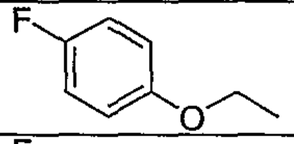
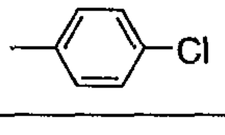
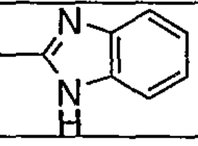
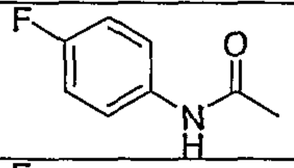
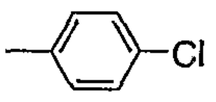
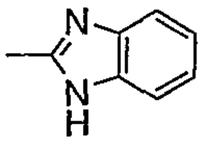
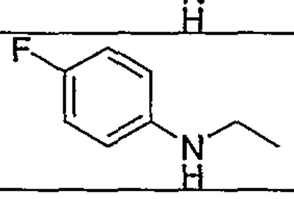
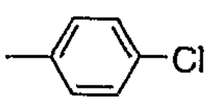
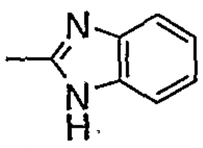
E627			
E628			
E629			
E630			
E631			
E632		CH_3	
E633			
E634			
E635			
E636			
E637		CH_3	
E638			
E639			

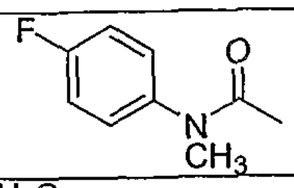
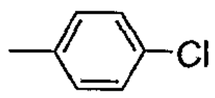
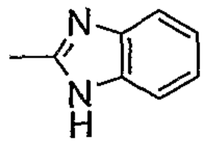
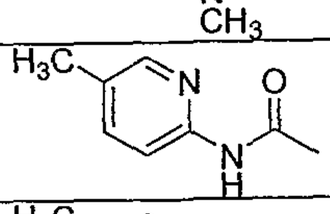
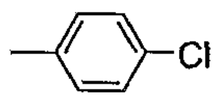
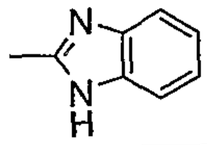
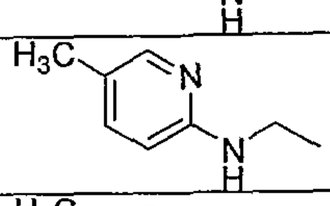
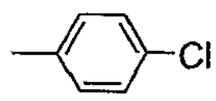
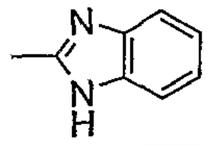
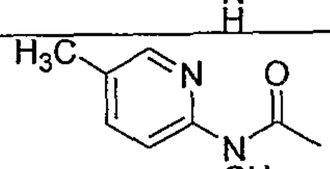
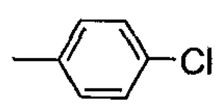
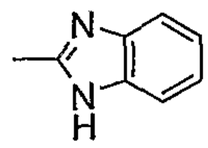
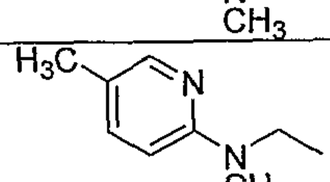
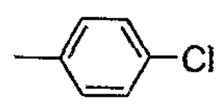
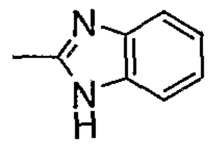
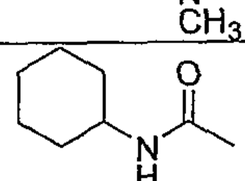
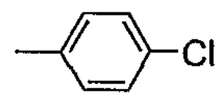
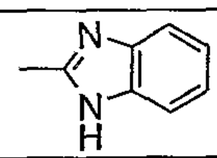
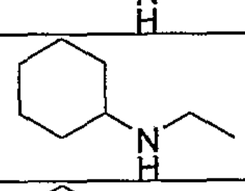
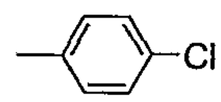
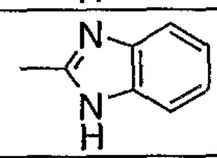
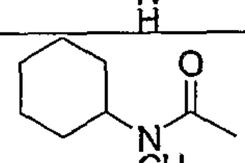
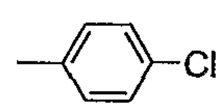
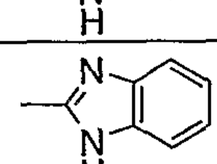
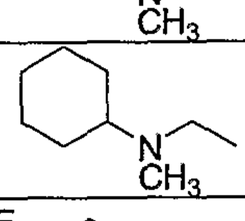
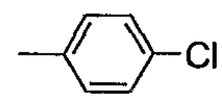
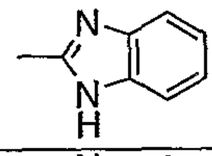
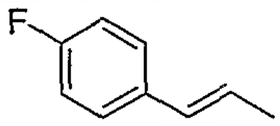
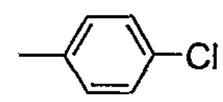
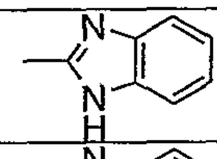
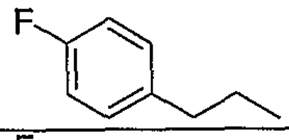
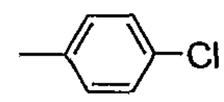
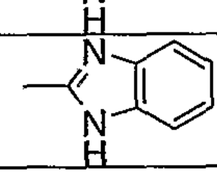
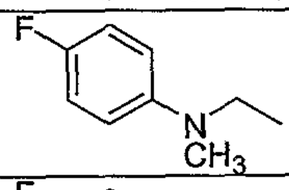
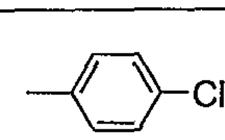
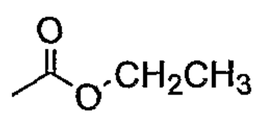
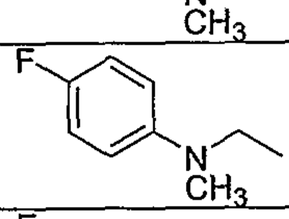
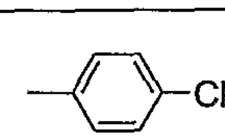
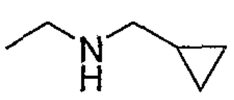
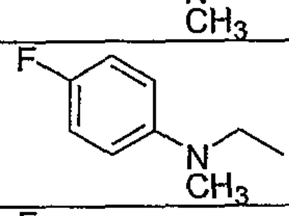
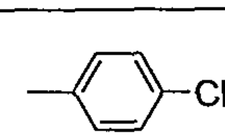
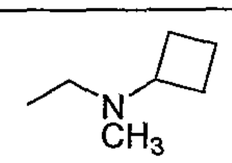
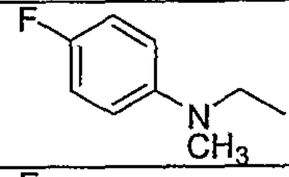
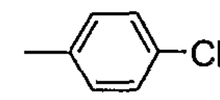
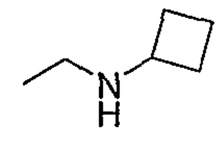
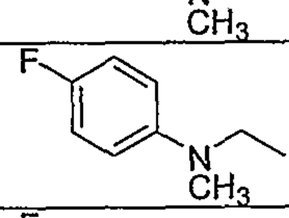
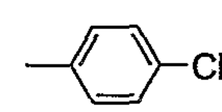
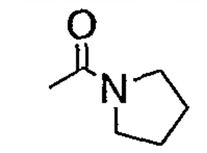
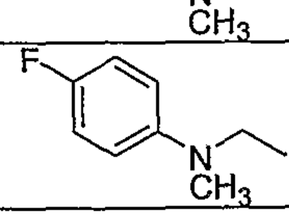
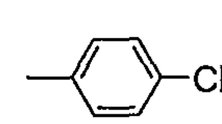
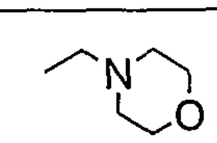
TABLE E-1G

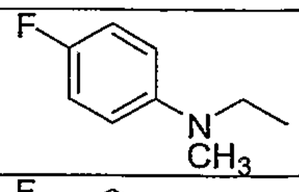
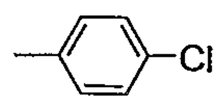
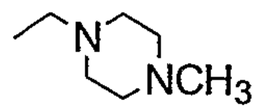
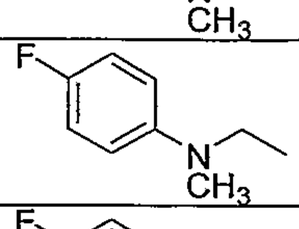
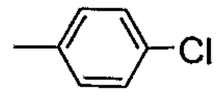
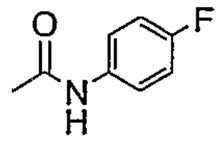
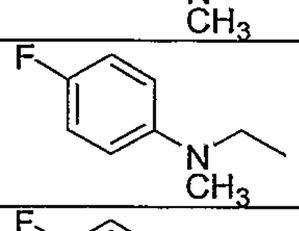
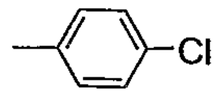
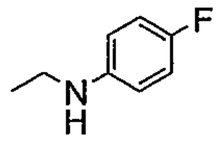
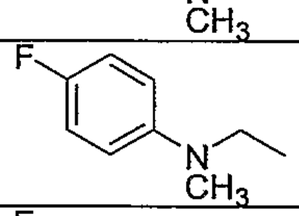
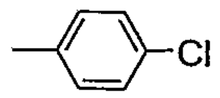
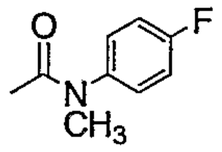
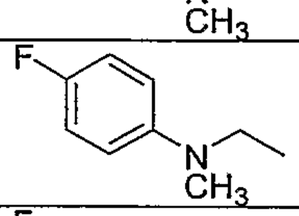
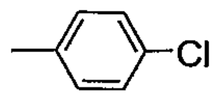
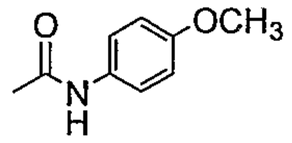
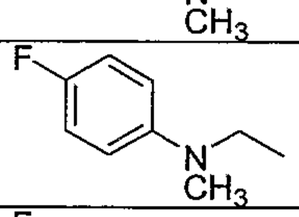
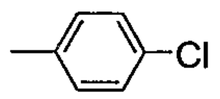
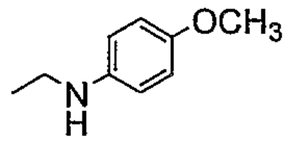
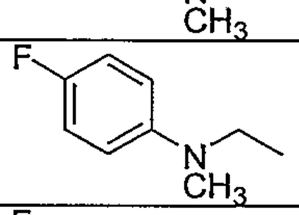
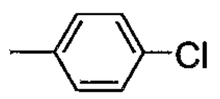
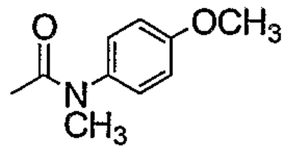
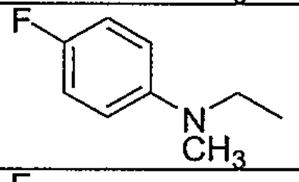
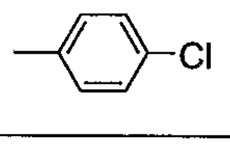
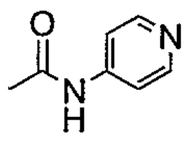
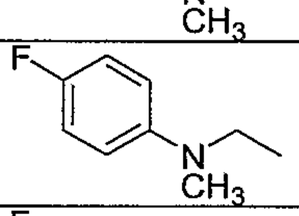
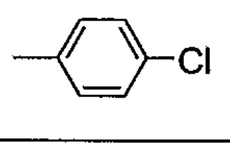
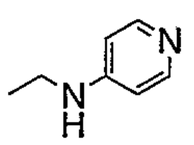
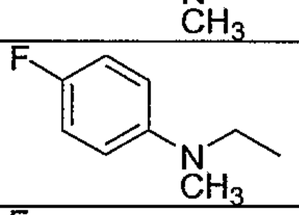
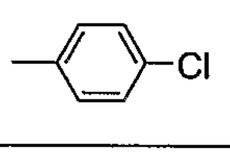
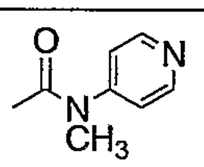
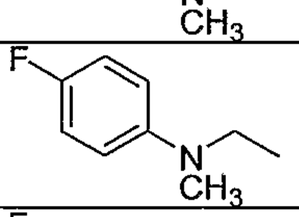
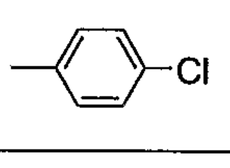
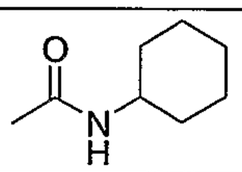
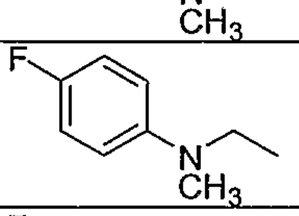
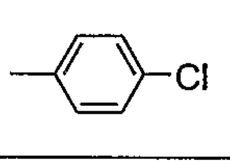
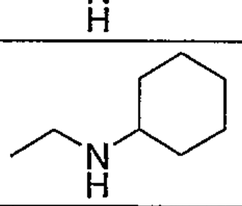
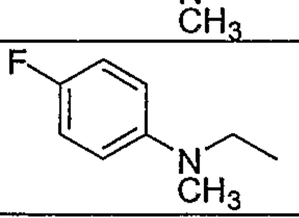
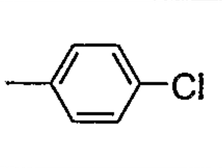
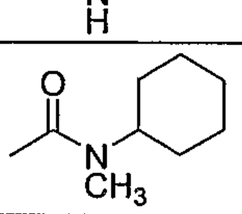
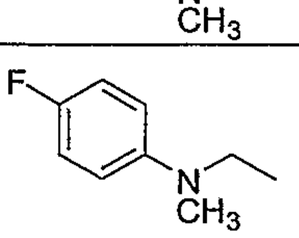
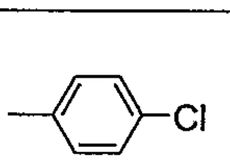
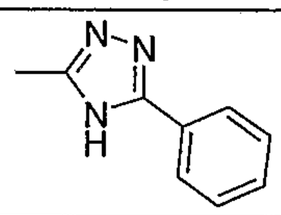
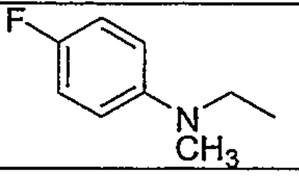
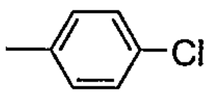
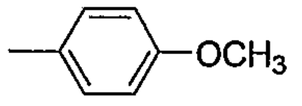


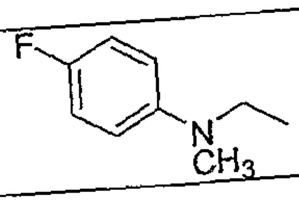
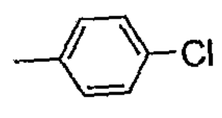
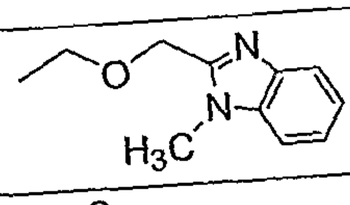
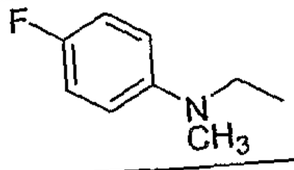
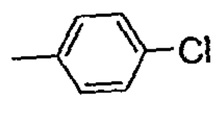
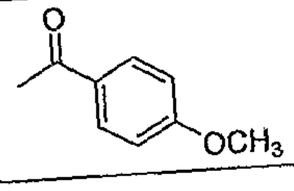
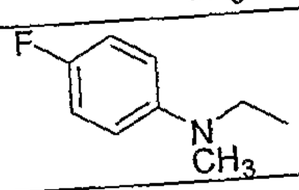
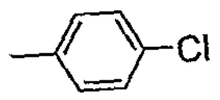
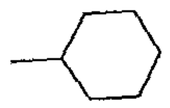
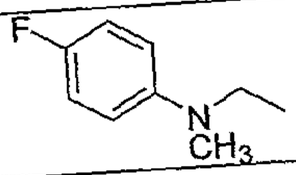
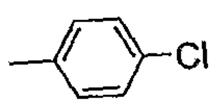
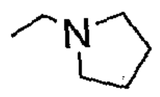
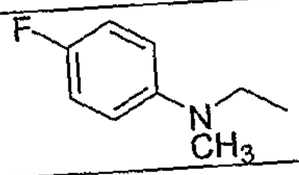
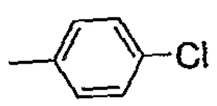
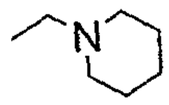
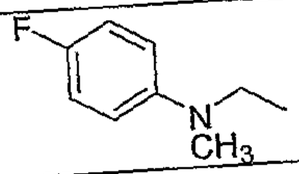
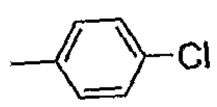
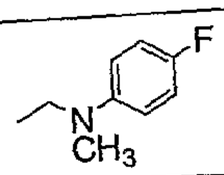
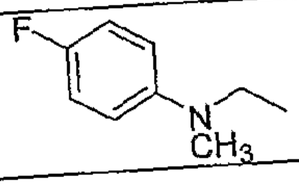
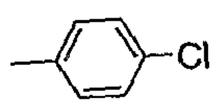
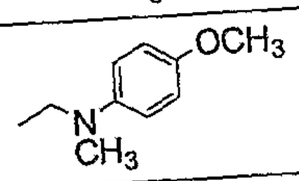
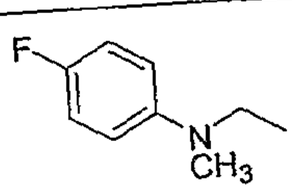
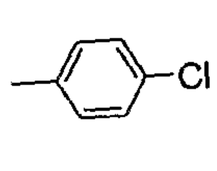
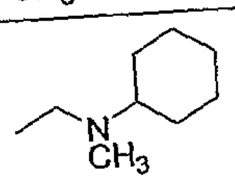
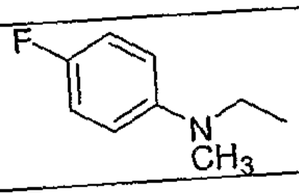
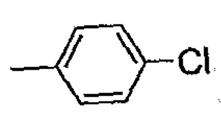
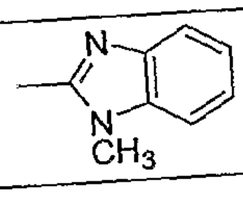
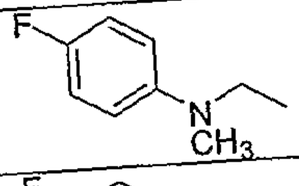
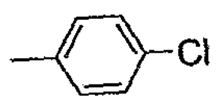
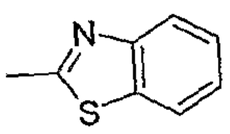
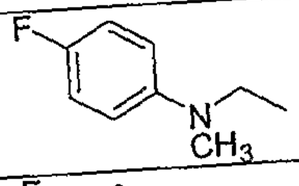
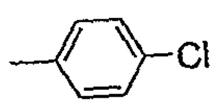
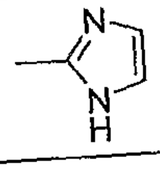
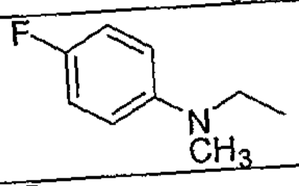
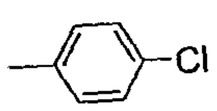
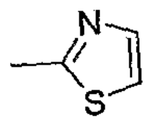
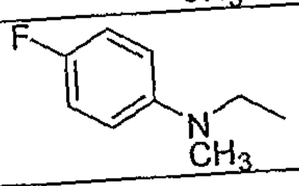
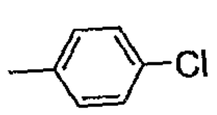
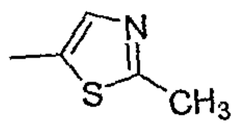
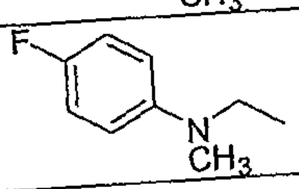
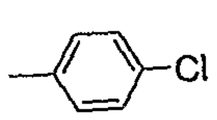
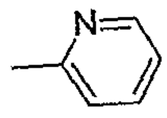
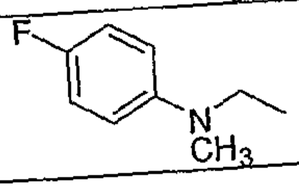
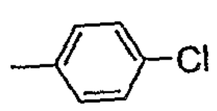
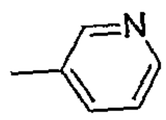
Cpd. No.	Ar^1-X-Y	R^1	R^2

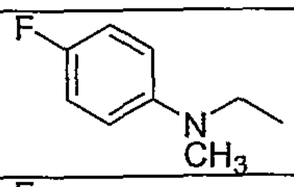
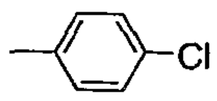
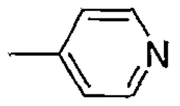
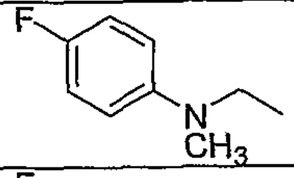
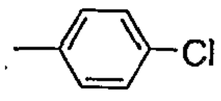
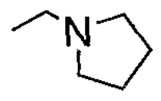
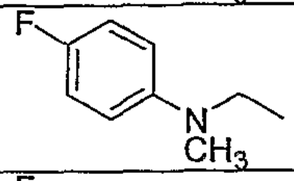
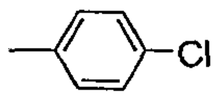
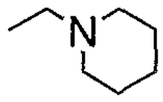
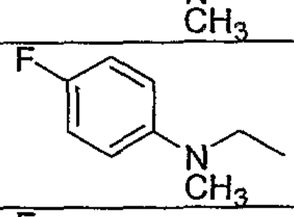
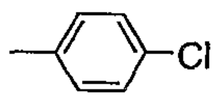
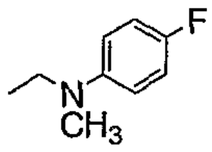
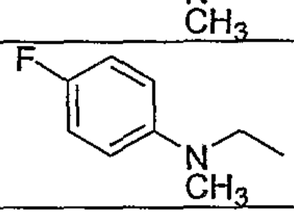
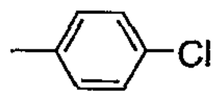
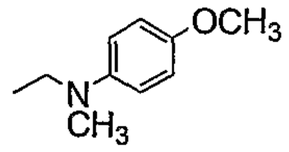
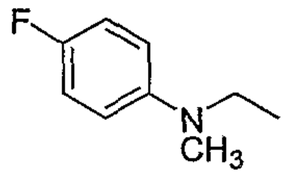
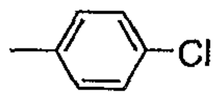
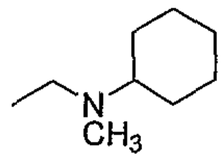
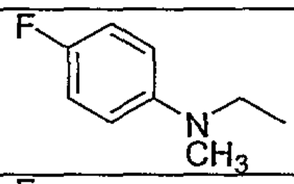
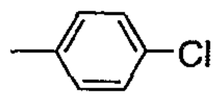
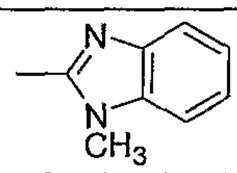
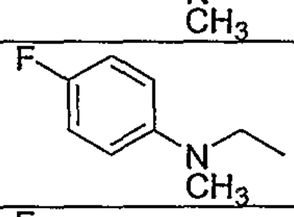
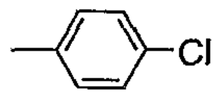
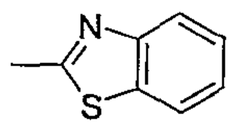
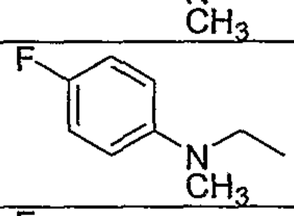
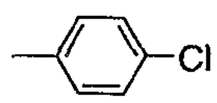
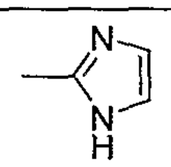
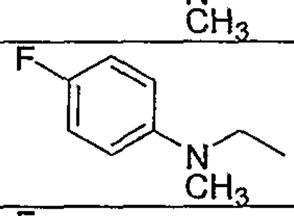
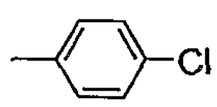
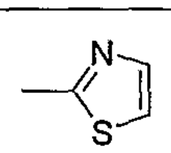
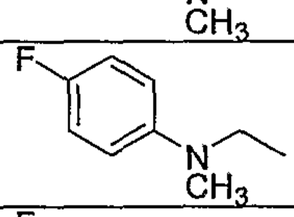
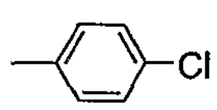
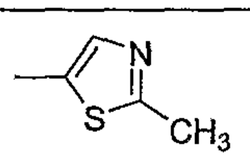
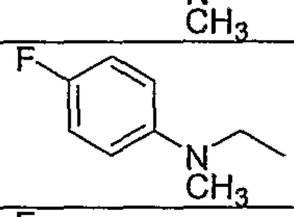
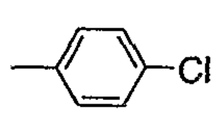
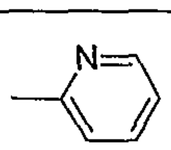
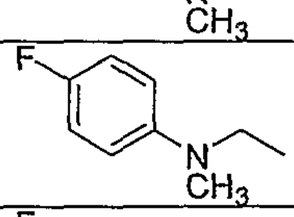
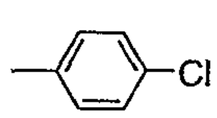
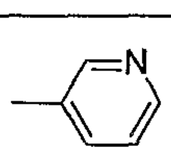
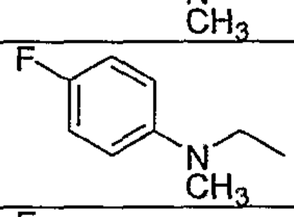
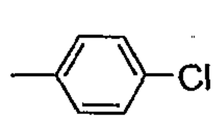
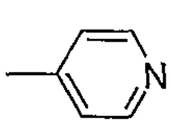
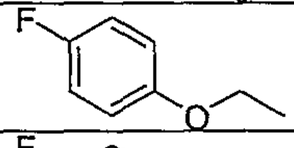
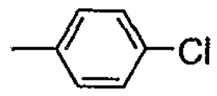
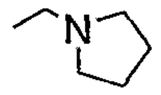
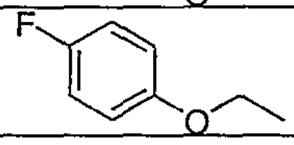
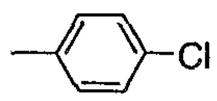
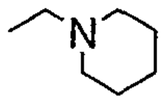
E640			
E641			
E642			
E643			
E644			
E645			
E646			
E647			
E648			
E649			
E650			
E651			
E652			
E653			
E654			
E655			
E656			

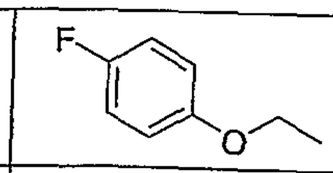
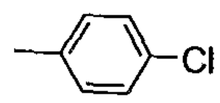
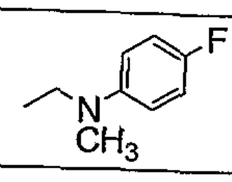
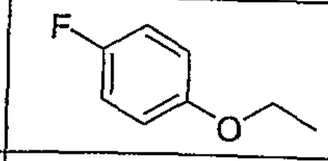
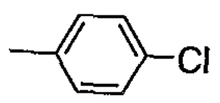
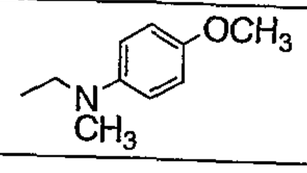
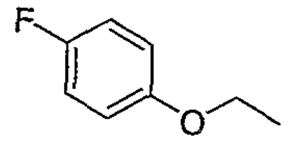
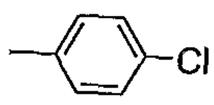
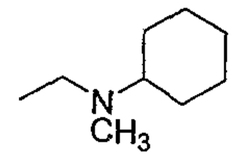
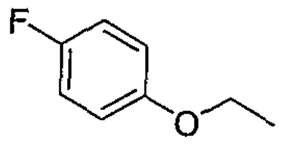
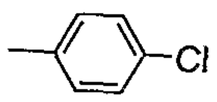
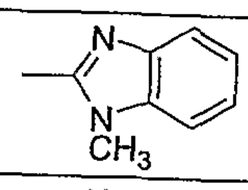
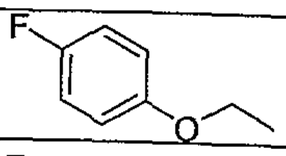
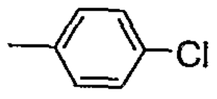
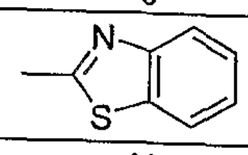
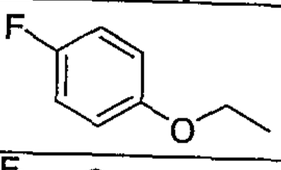
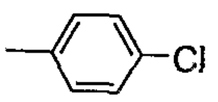
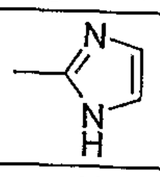
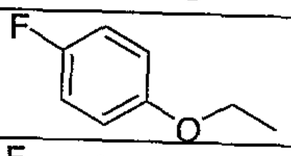
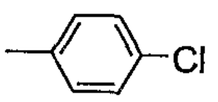
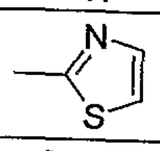
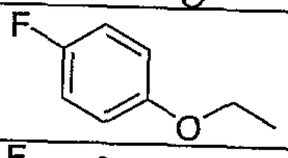
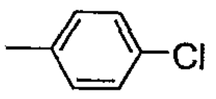
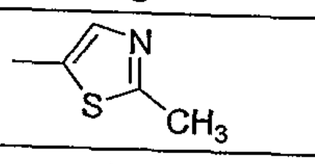
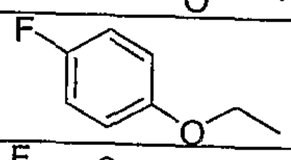
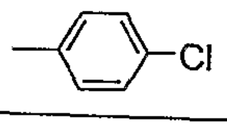
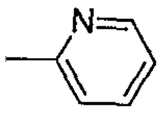
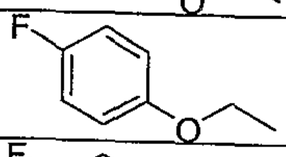
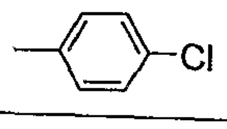
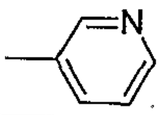
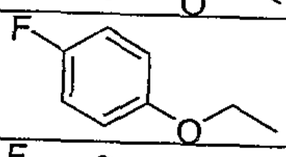
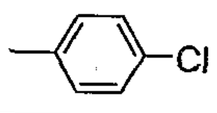
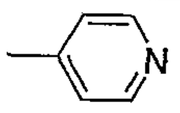
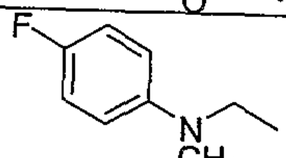
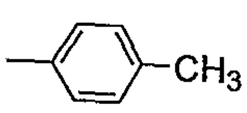
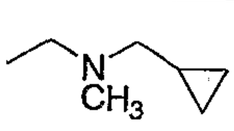
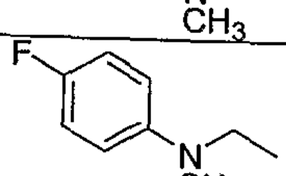
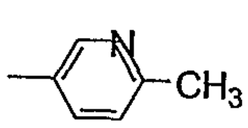
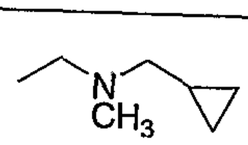
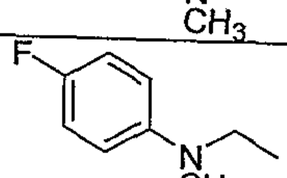
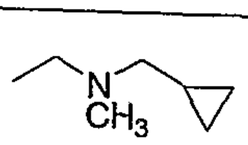
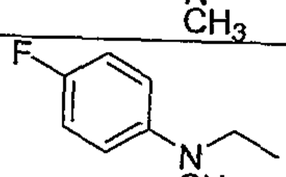
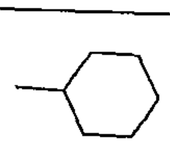
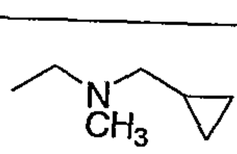
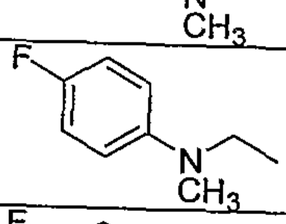
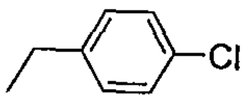
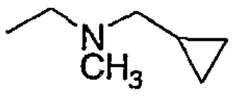
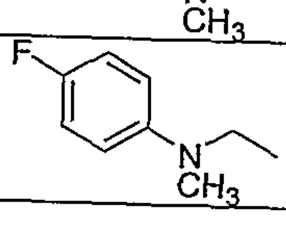
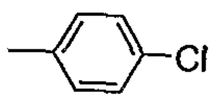
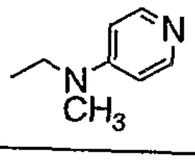
E657			
E658			
E659			
E660			
E661			
E662			
E663			
E664			
E665			
E666			
E667			
E668			
E669			
E670			
E671			
E672			
E673			

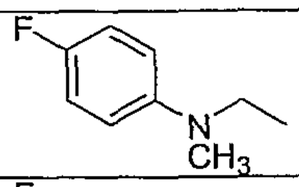
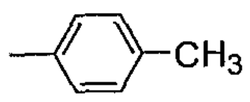
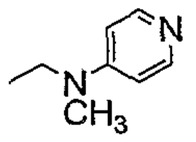
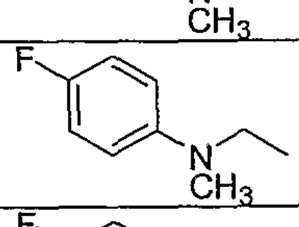
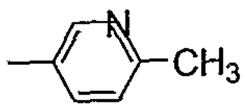
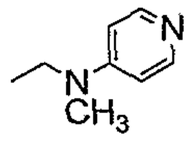
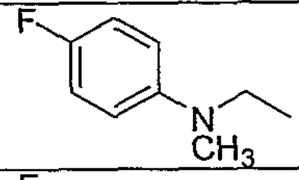
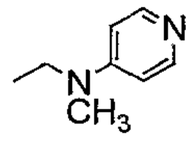
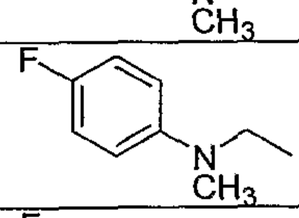
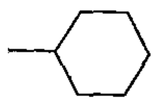
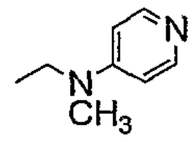
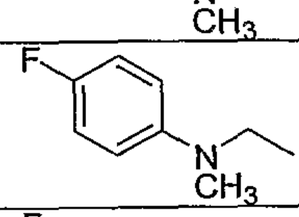
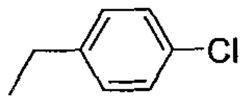
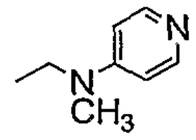
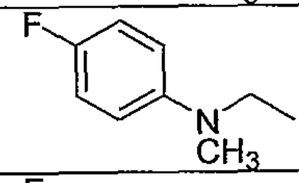
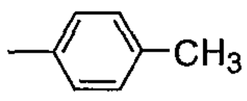
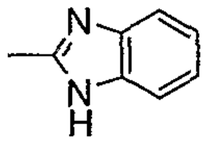
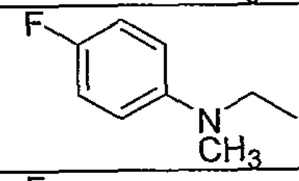
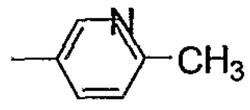
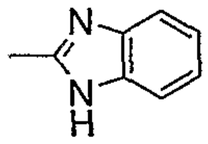
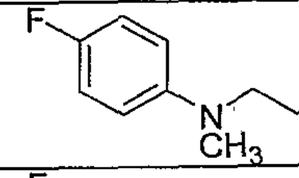
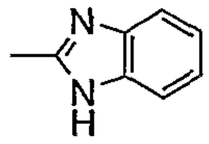
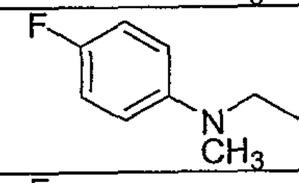
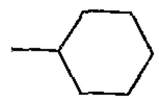
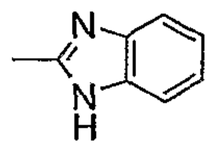
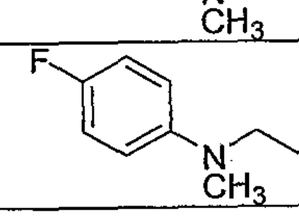
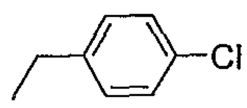
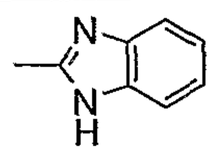
E674			
E675			
E676			
E677			
E678			
E679			
E680			
E681			
E682			
E683			
E684			
E685			
E686			
E687			
E688			
E689			
E690			

E691			
E692			
E693			
E694			
E695			
E696			
E697			
E698			
E699			
E700			
E701			
E702			
E703			
E704			
E705			

E706			
E707			
E708			
E709			
E710			
E711			
E712			
E713			
E714			
E715			
E716			
E717			
E718			
E719			
E720			

E721			
E722			
E723			
E724			
E725			
E726			
E727			
E728			
E729			
E730			
E731			
E732			
E733			
E734			
E735			
E736			

E737			
E738			
E739			
E740			
E741			
E742			
E743			
E744			
E745			
E746			
E747			
E748			
E749			
E750		CH_3	
E751			
E752			
E753			

E754			
E755			
E756		CH_3	
E757			
E758			
E759			
E760			
E761		CH_3	
E762			
E763			

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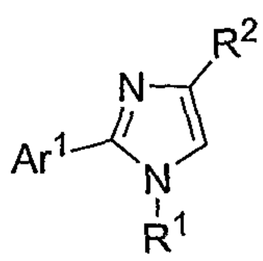

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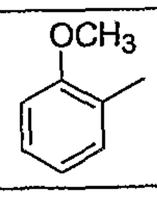
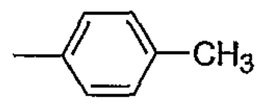
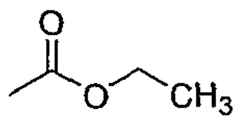
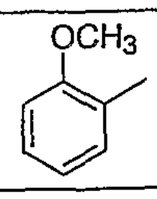
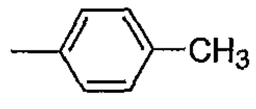
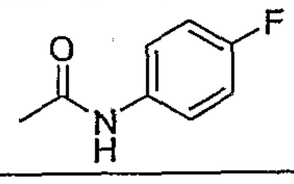
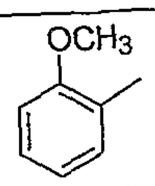
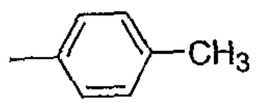
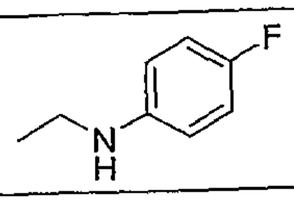
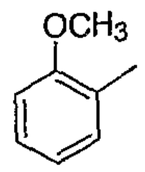
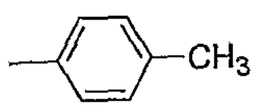
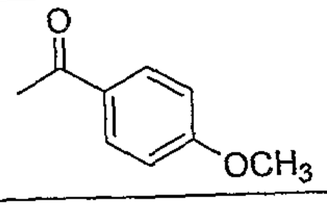
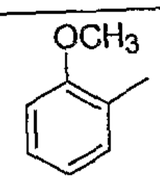
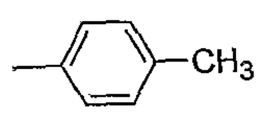
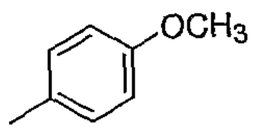
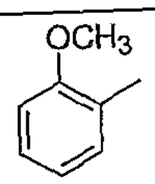
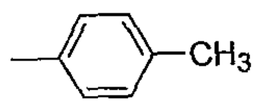
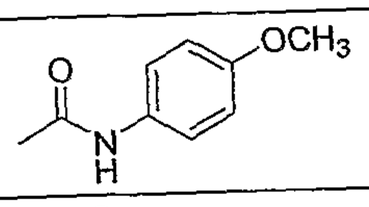
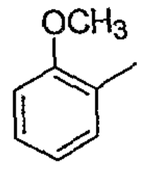
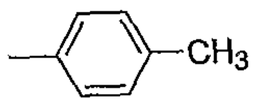
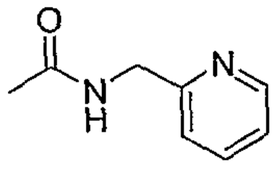
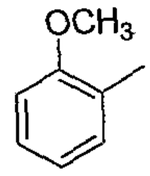
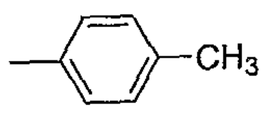
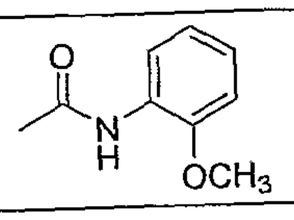
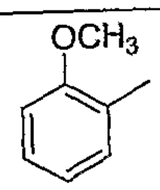
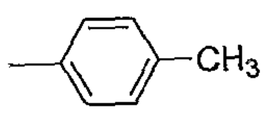
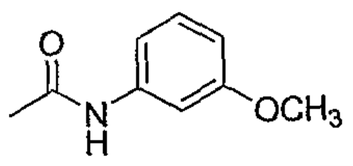
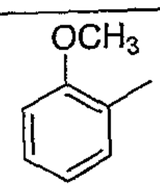
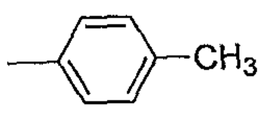
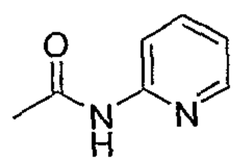
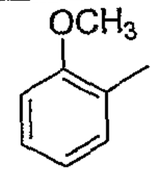
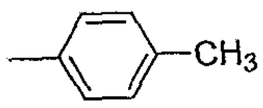
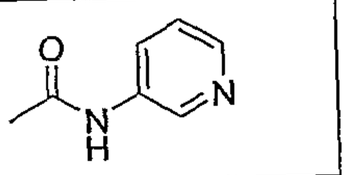
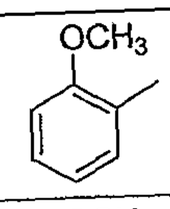
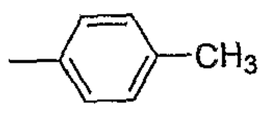
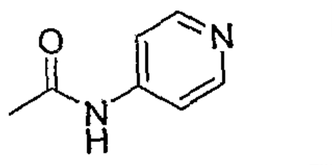
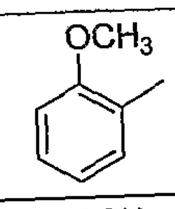
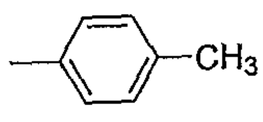
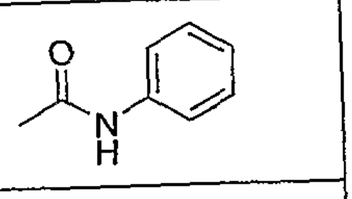
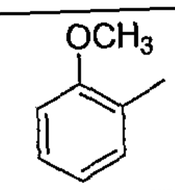
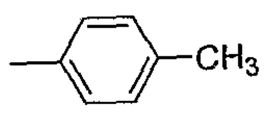
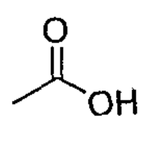
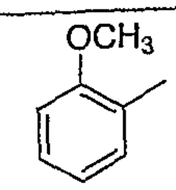
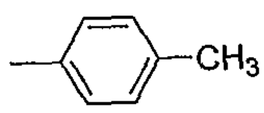
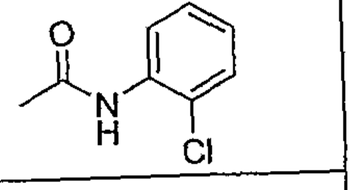
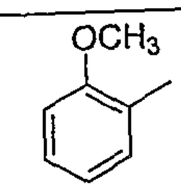
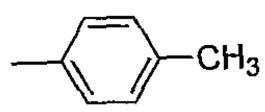
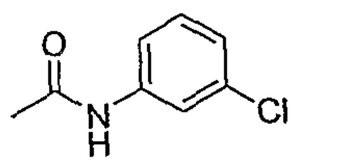
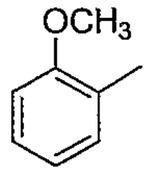
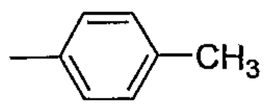
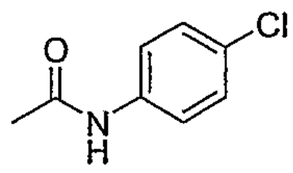
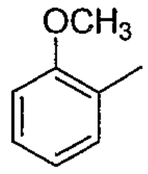
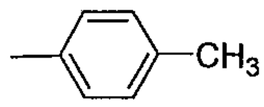
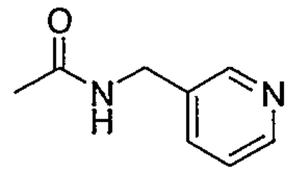
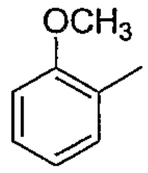
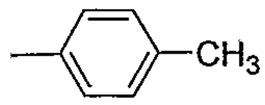
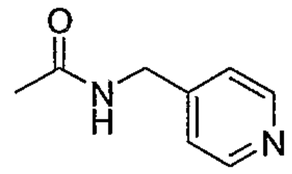
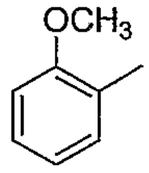
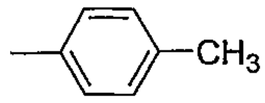
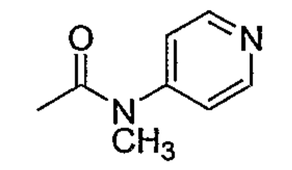
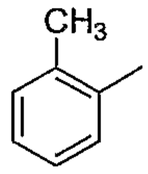
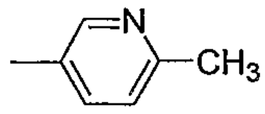
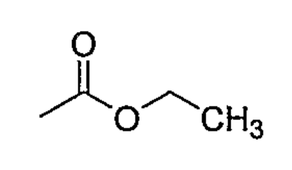
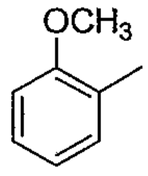
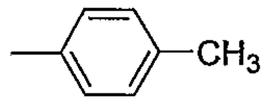
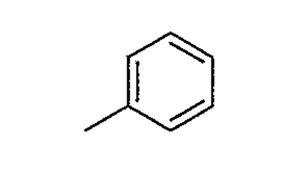
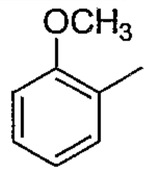
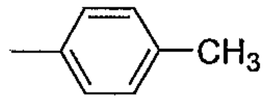
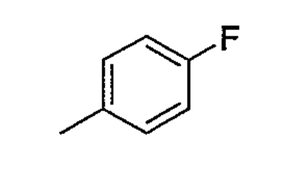
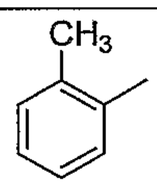
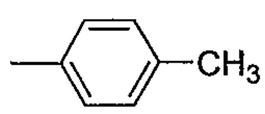
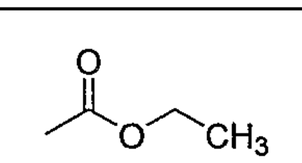
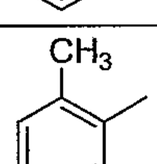
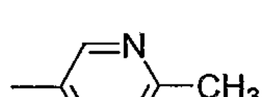
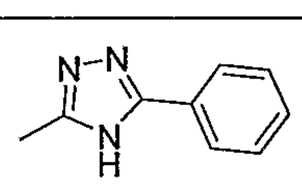
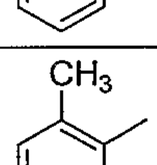
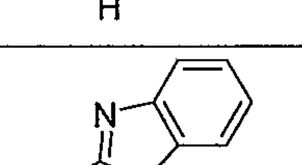
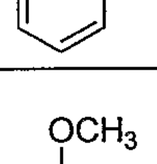
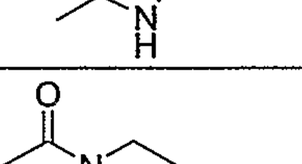
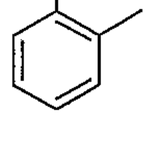
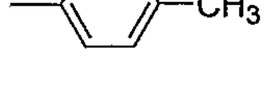
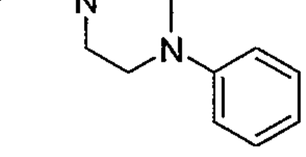
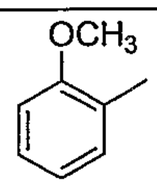
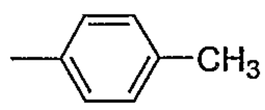
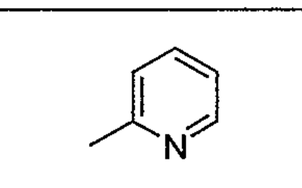
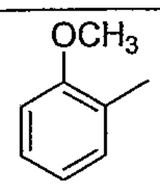
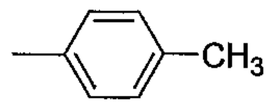
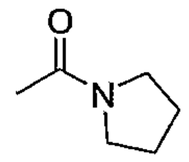
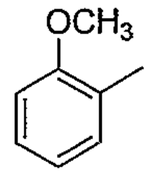
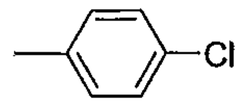
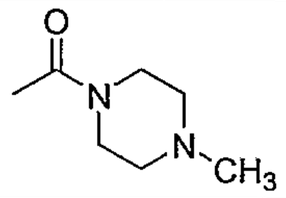
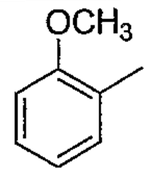
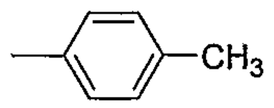
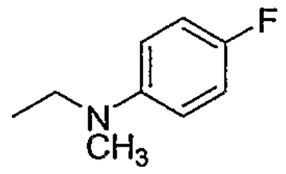
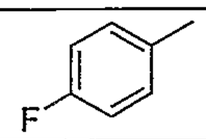
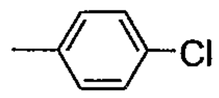
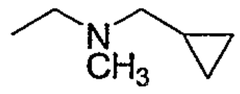
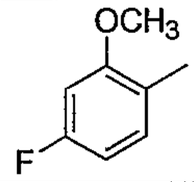
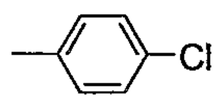
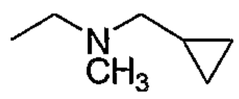
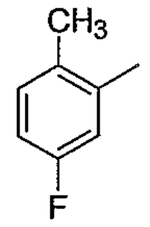
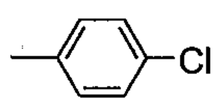
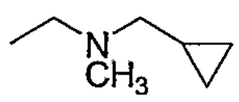
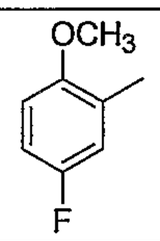
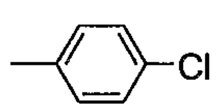
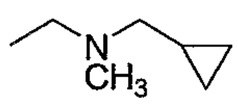
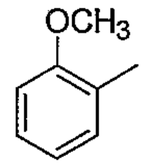
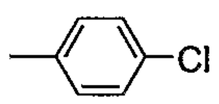
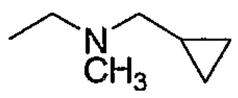
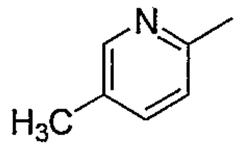
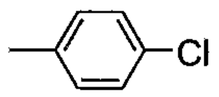
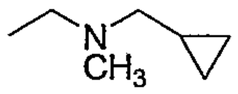
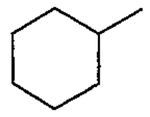
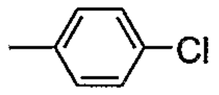
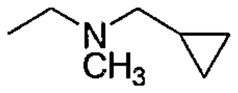
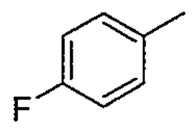
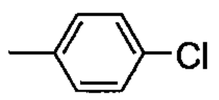
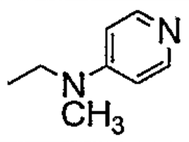
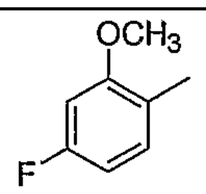
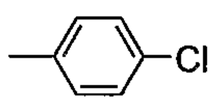
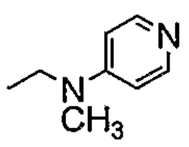
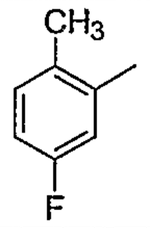
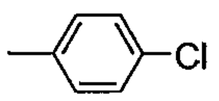
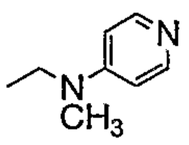
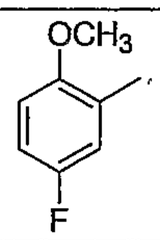
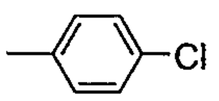
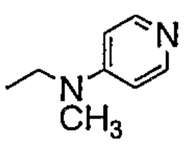
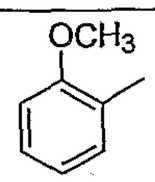
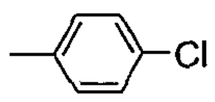
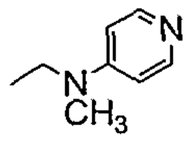
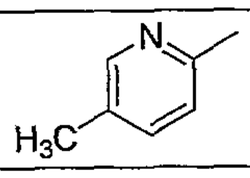
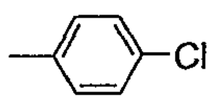
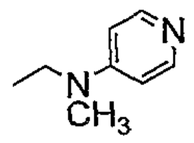
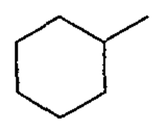
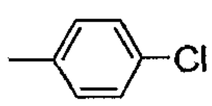
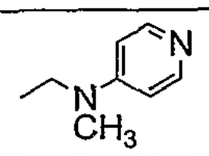
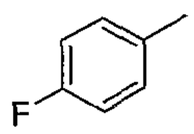
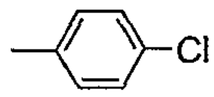
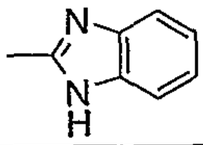
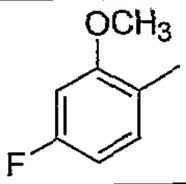
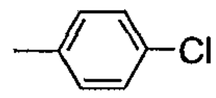
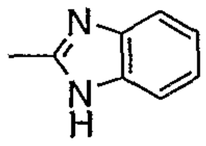
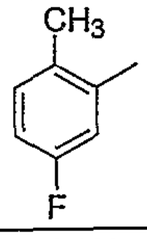
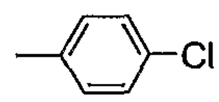
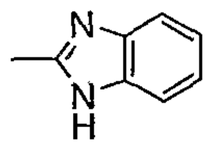
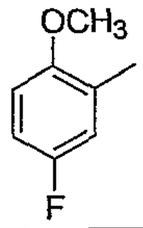
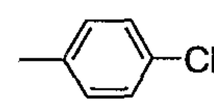
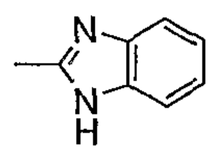
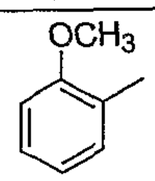
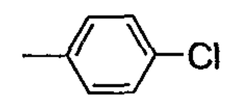
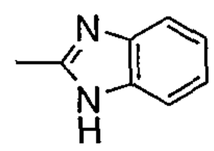
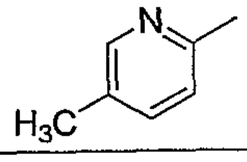
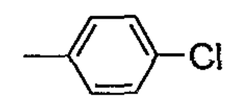
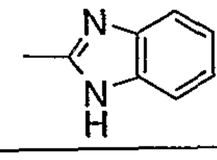
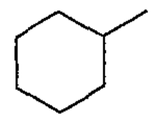
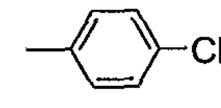
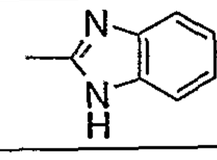
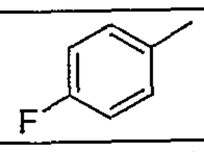
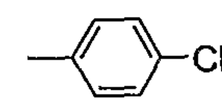
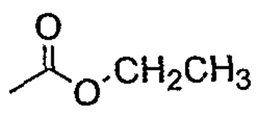
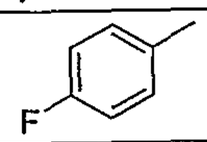
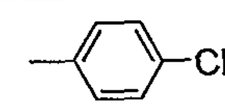
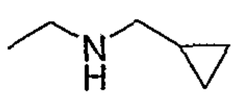
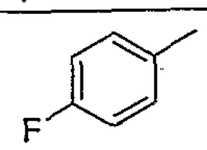
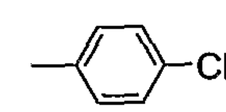
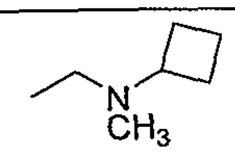
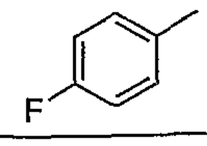
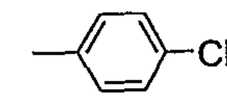
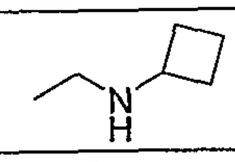
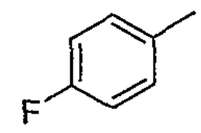
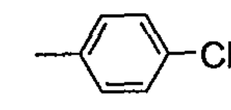
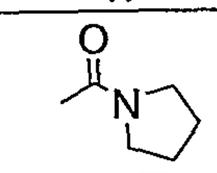
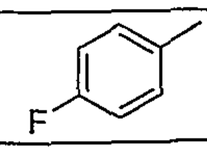
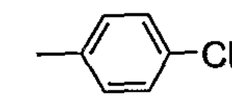
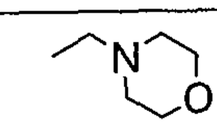
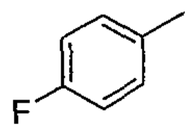
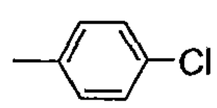
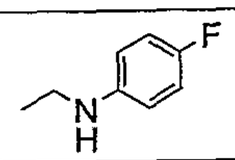
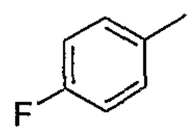
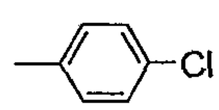
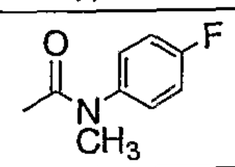
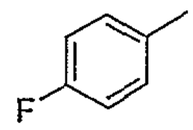
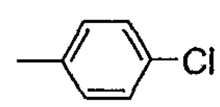
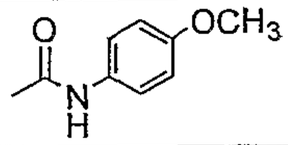
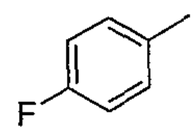
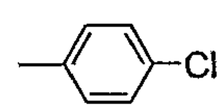
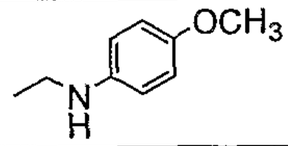
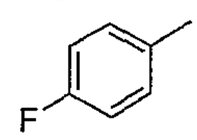
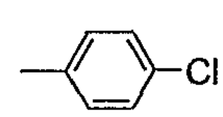
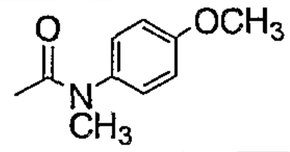
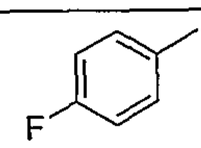
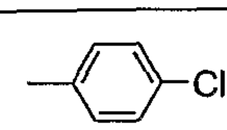
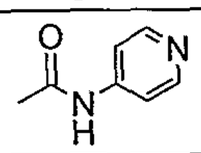
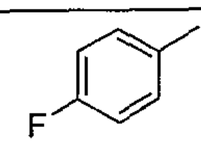
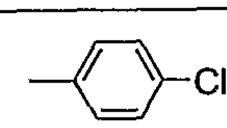
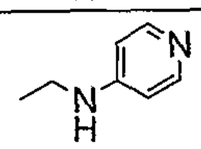
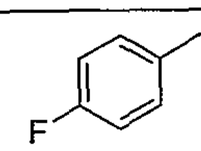
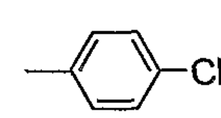
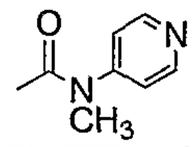
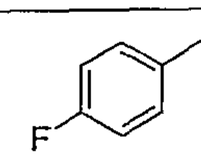
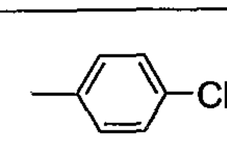
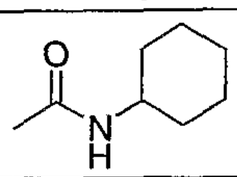
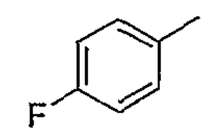
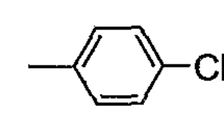
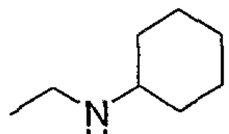
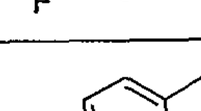
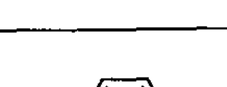
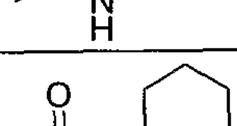
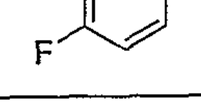
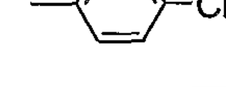
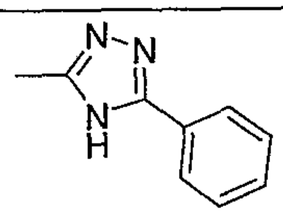
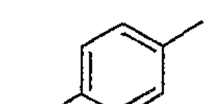
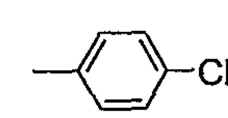
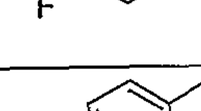
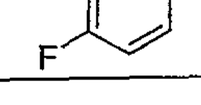
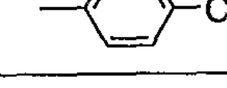
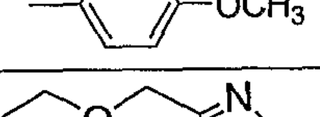
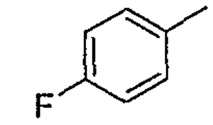
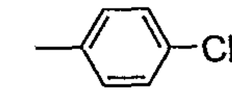
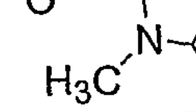
F1			
F2			

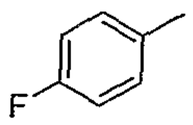
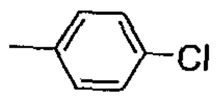
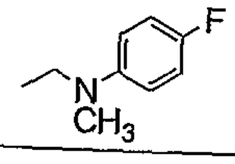
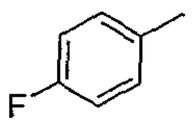
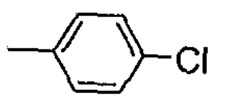
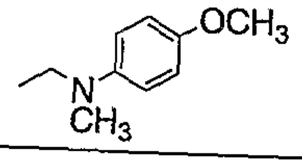
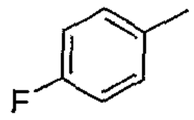
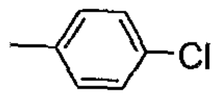
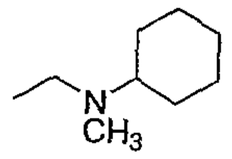
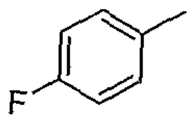
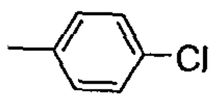
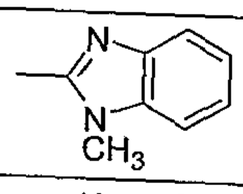
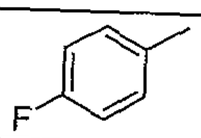
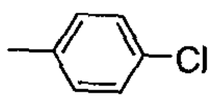
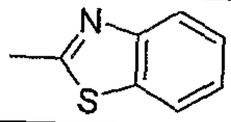
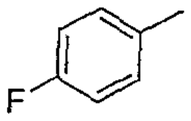
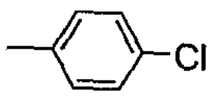
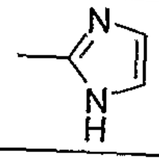
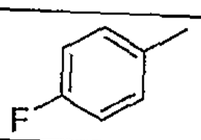
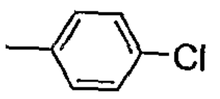
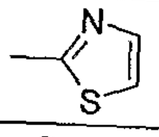
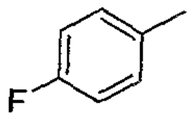
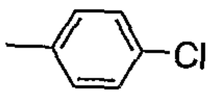
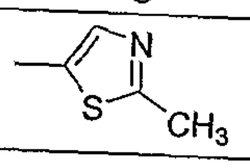
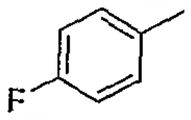
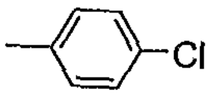
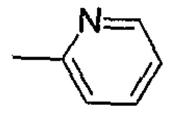
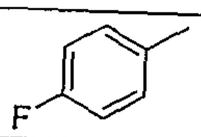
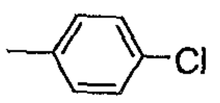
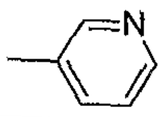
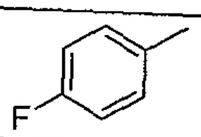
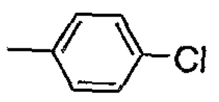
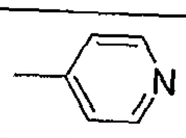
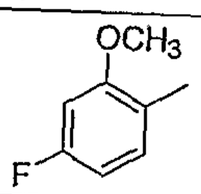
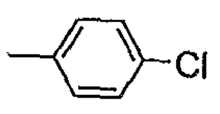
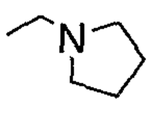
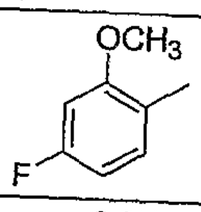
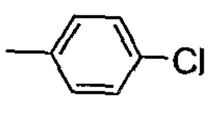
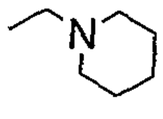
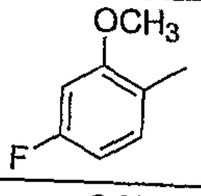
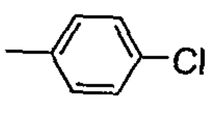
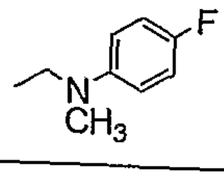
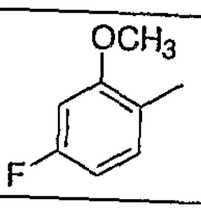
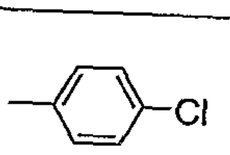
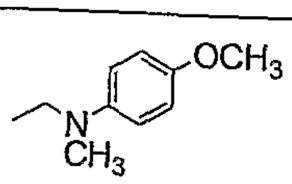
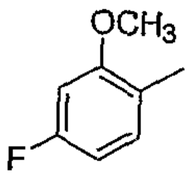
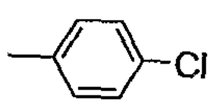
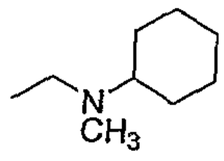
F3			
F4			
F5			
F6			
F7			
F8			
F9			
F10			
F11			
F12			
F13			
F14			
F15			
F16			

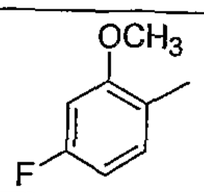
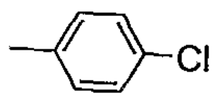
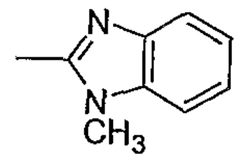
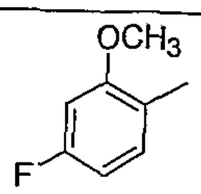
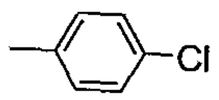
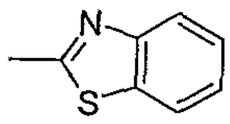
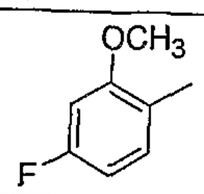
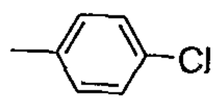
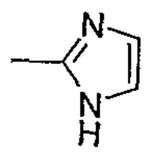
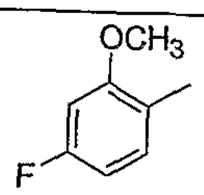
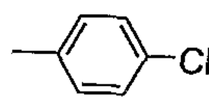
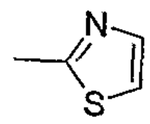
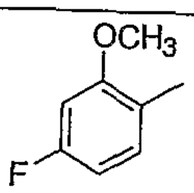
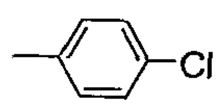
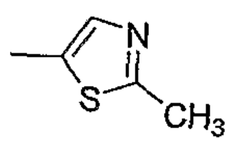
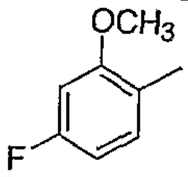
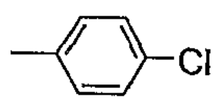
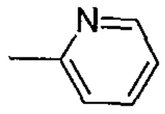
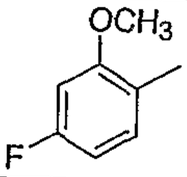
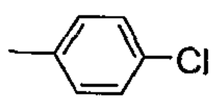
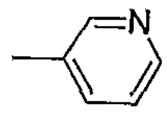
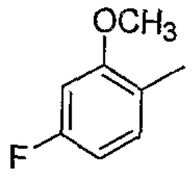
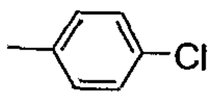
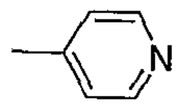
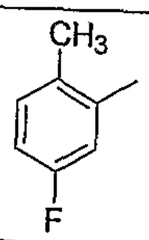
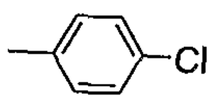
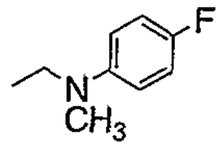
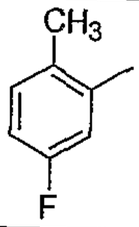
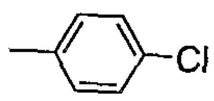
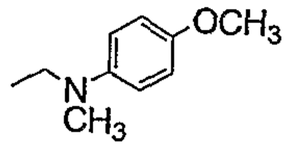
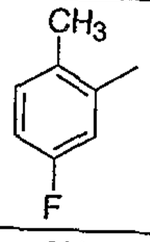
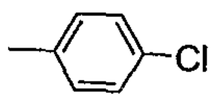
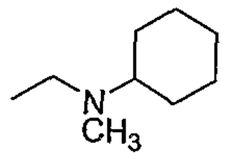
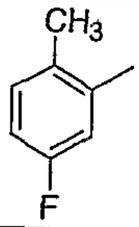
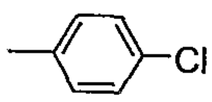
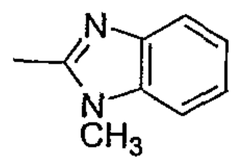
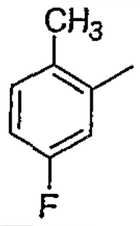
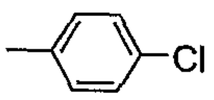
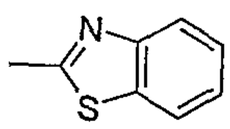
F17			
F18			
F19			
F20			
F21			
F22			
F23			
F24			
F25			
F26			
F27			
F28			
F29			

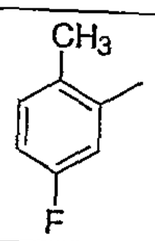
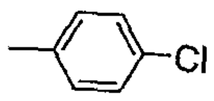
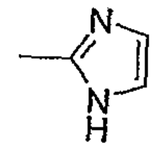
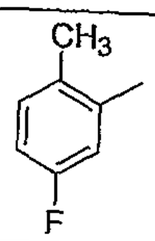
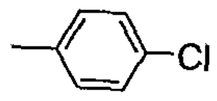
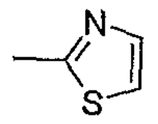
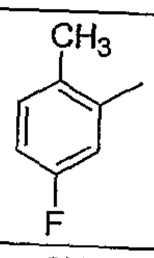
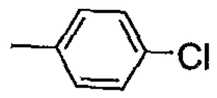
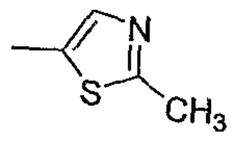
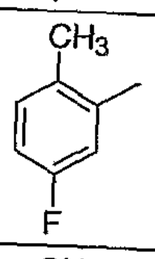
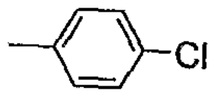
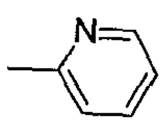
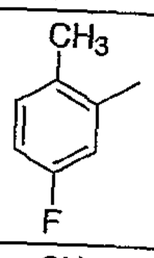
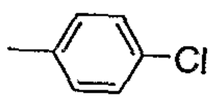
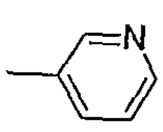
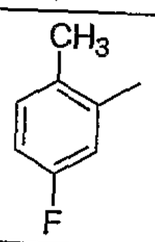
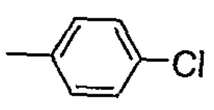
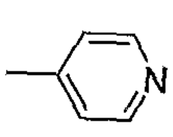
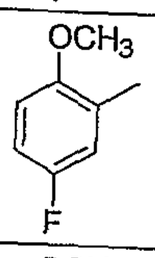
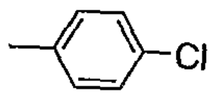
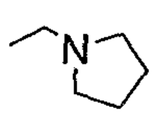
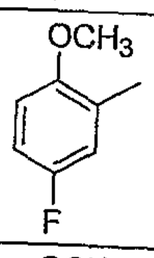
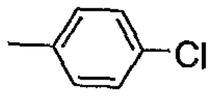
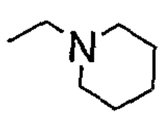
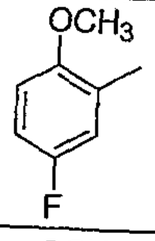
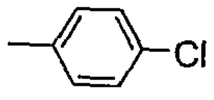
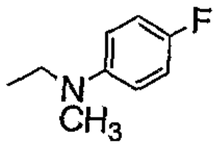
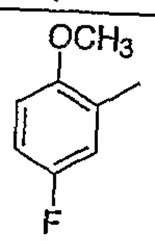
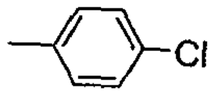
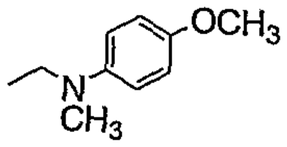
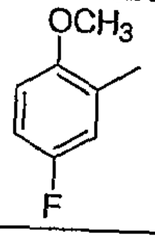
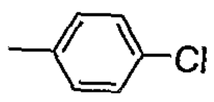
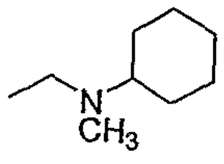
F30			
F31			
F32			
F33			
F34			
F35			
F36			
F37			
F38			
F39			
F40			
F41			
F42			
F43			

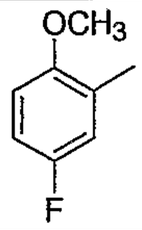
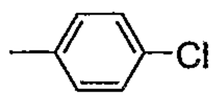
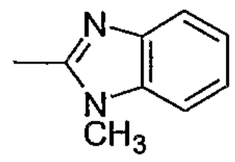
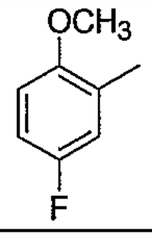
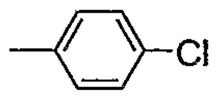
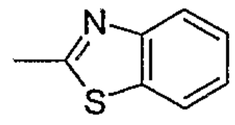
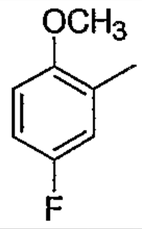
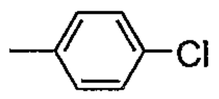
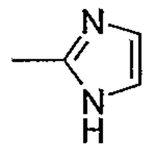
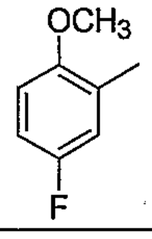
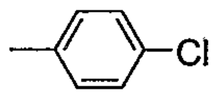
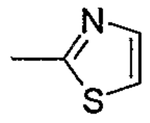
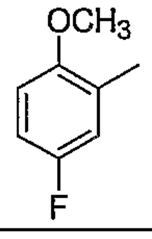
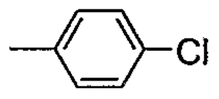
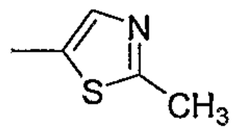
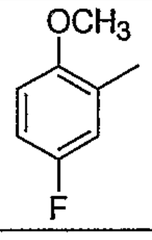
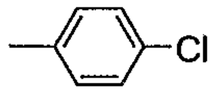
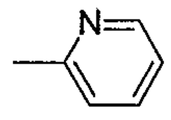
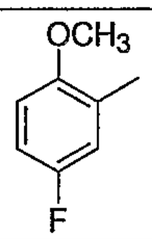
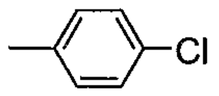
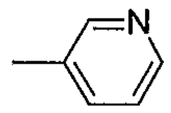
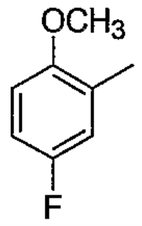
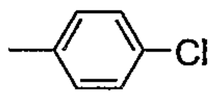
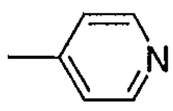
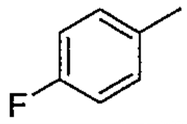
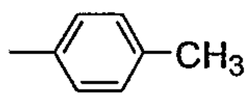
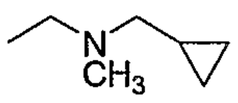
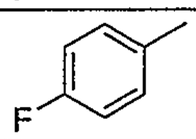
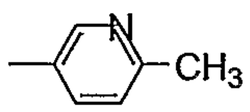
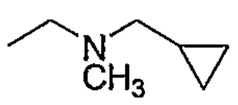
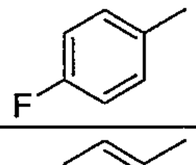
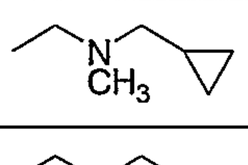
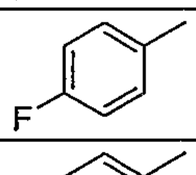
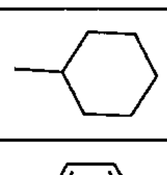
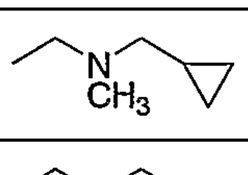
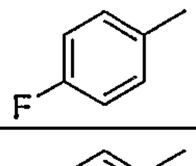
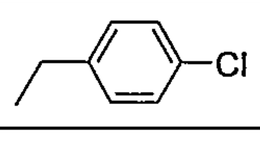
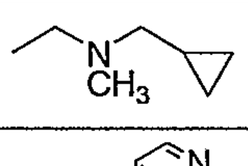
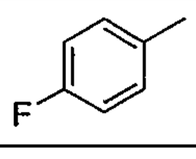
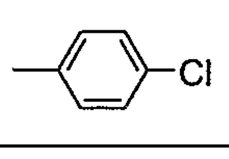
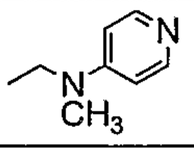
F44			
F45			
F46			
F47			
F48			
F49			
F50			
F51			
F52			
F53			
F54			
F55			
F56			
F57			
F58			
F59			

F60			
F61			
F62			
F63			
F64			
F65			
F66			
F67			
F68			
F69			
F70			
F71			
F72			
F73			
F74			
F75			

F76			
F77			
F78			
F79			
F80			
F81			
F82			
F83			
F84			
F85			
F86			
F87			
F88			
F89			
F90			
F91			

F92			
F93			
F94			
F95			
F96			
F97			
F98			
F99			
F100			
F101			
F102			
F103			
F104			

F105			
F106			
F107			
F108			
F109			
F110			
F111			
F112			
F113			
F114			
F115			

F116			
F117			
F118			
F119			
F120			
F121			
F122			
F123			
F124			
F125			
F126		CH_3	
F127			
F128			
F129			

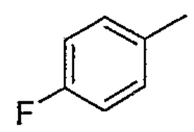
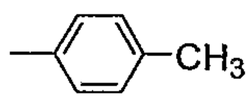
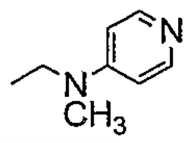
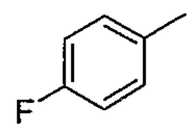
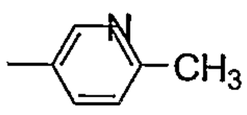
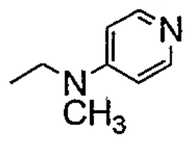
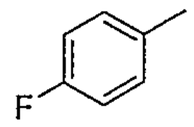
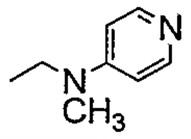
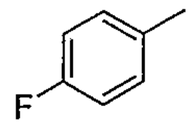
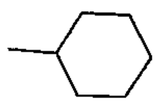
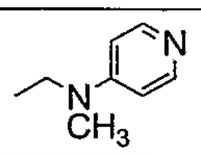
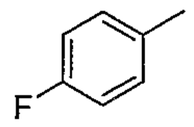
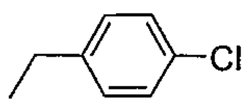
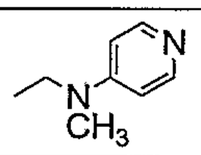
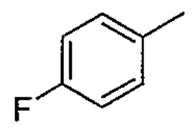
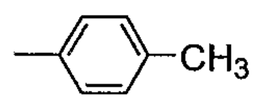
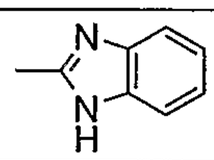
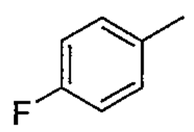
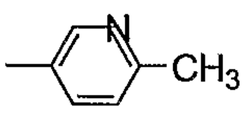
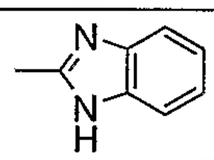
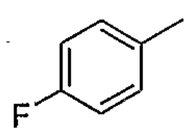
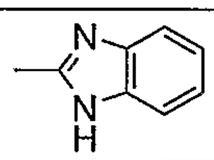
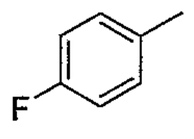
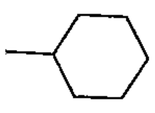
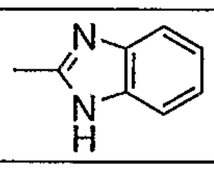
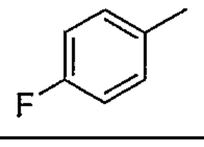
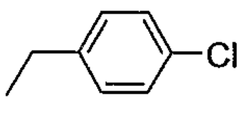
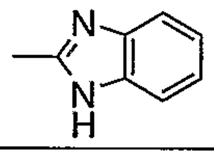
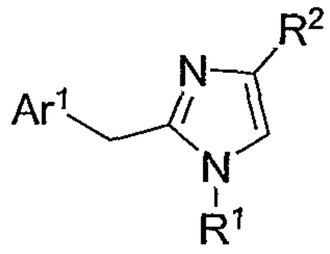
F130			
F131			
F132		CH_3	
F133			
F134			
F135			
F136			
F137		CH_3	
F139			
F140			

TABLE G-1A



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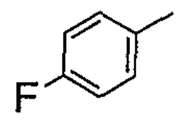
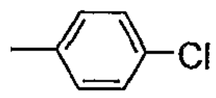
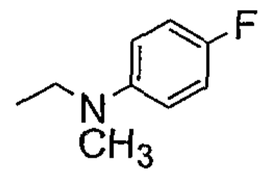
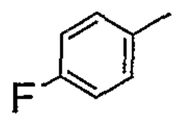
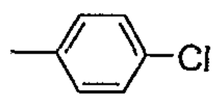
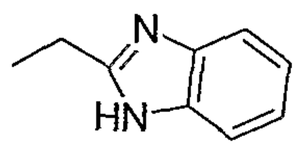
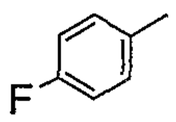
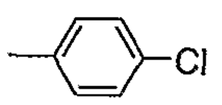
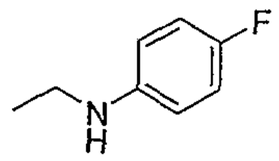
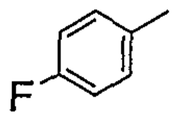
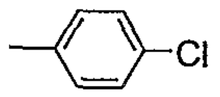
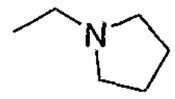
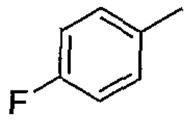
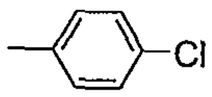
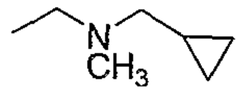
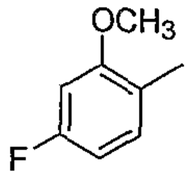
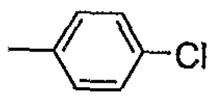
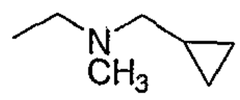
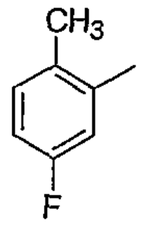
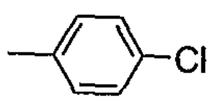
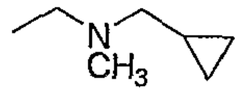
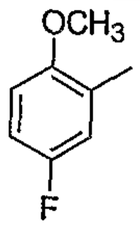
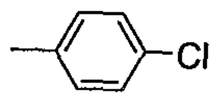
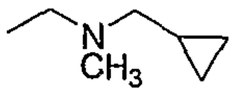
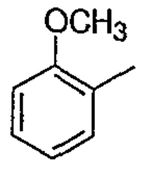
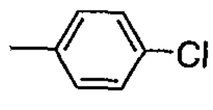
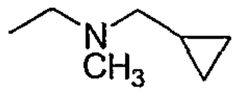
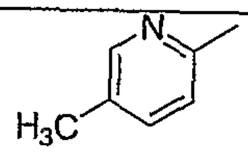
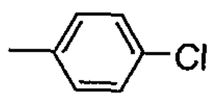
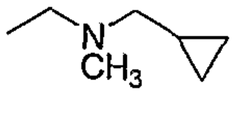
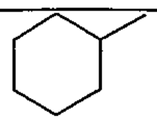
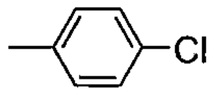
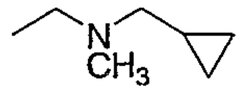
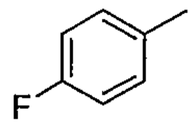
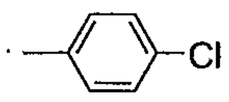
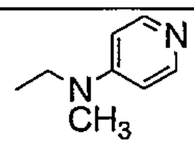
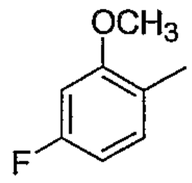
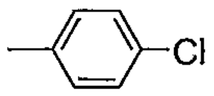
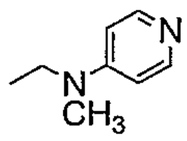
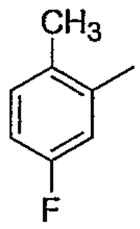
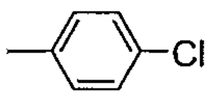
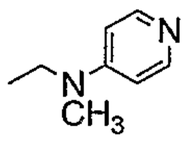
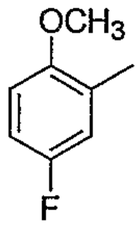
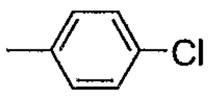
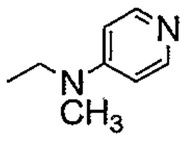
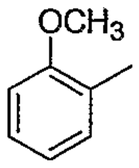
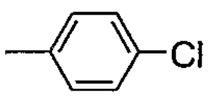
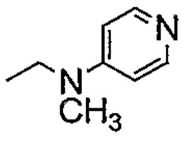
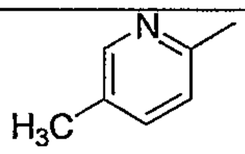
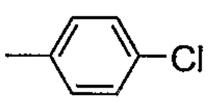
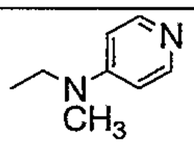
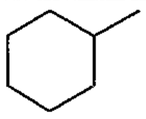
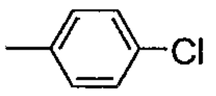
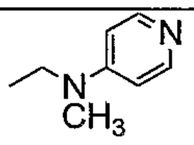
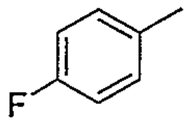
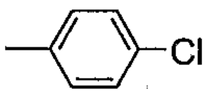
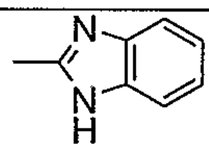
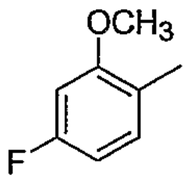
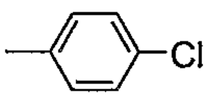
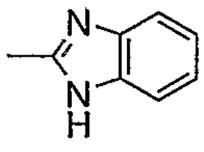
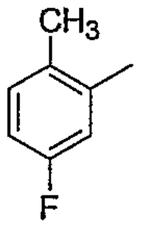
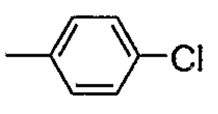
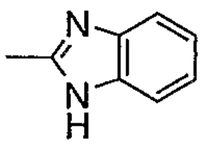
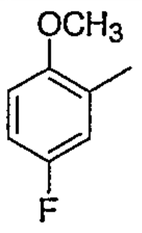
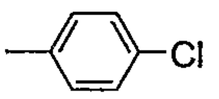
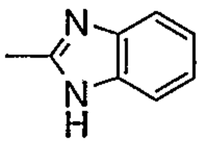
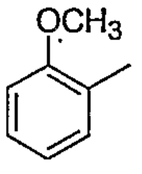
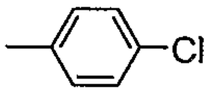
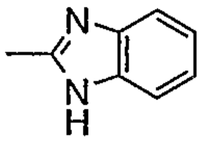
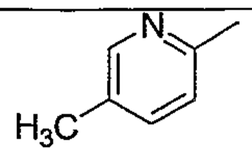
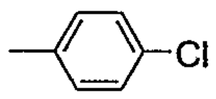
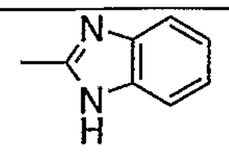
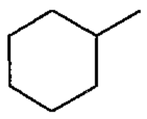
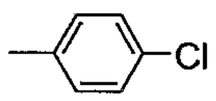
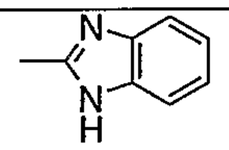
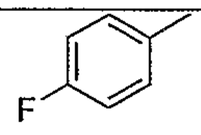
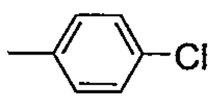
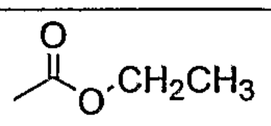
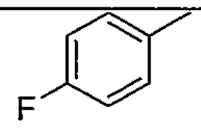
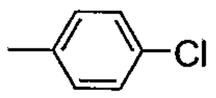
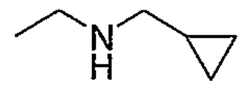
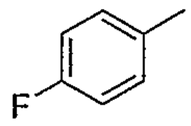
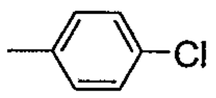
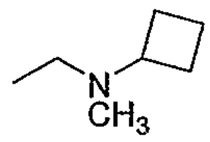
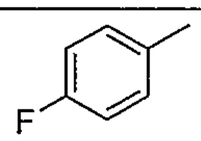
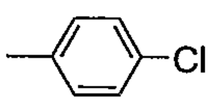
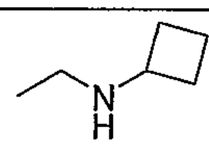
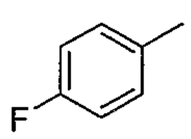
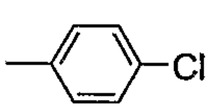
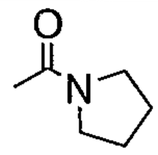
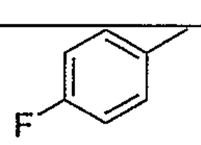
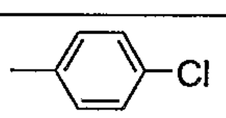
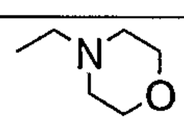
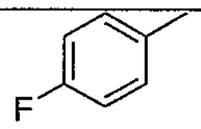
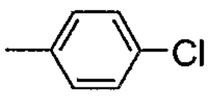
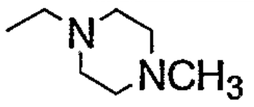
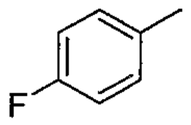
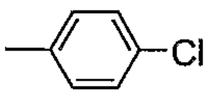
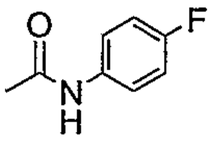
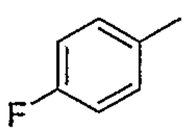
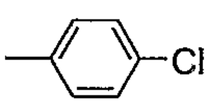
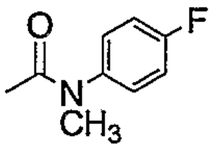
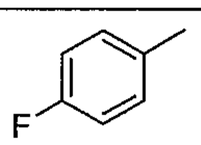
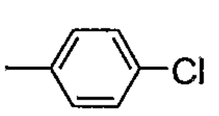
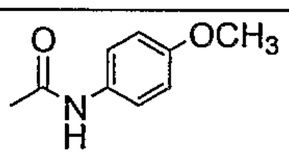
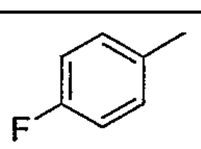
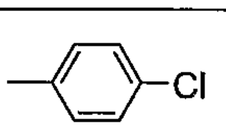
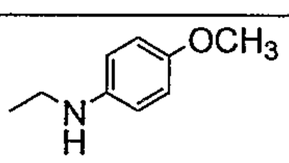
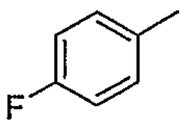
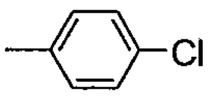
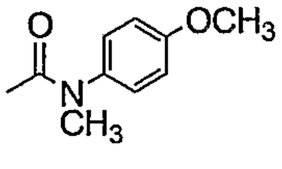
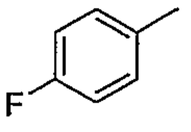
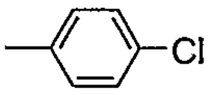
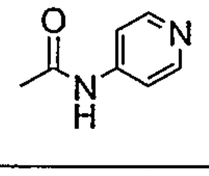
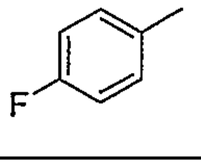
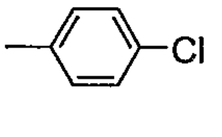
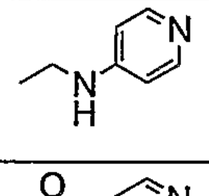
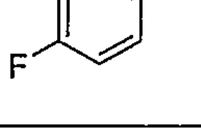
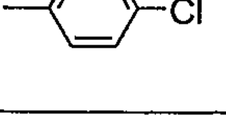
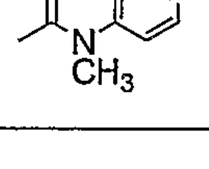
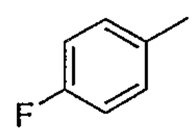
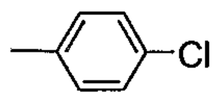
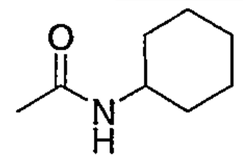
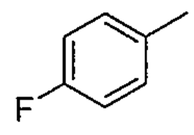
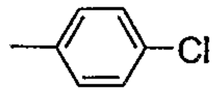
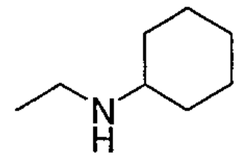
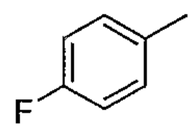
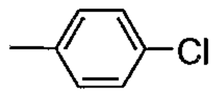
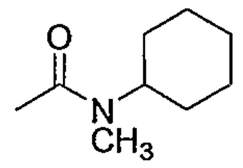
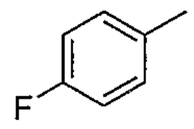
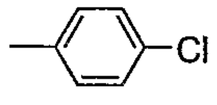
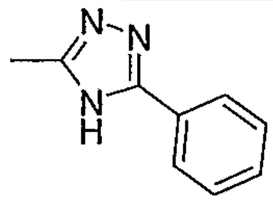
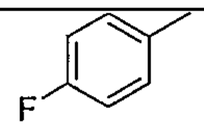
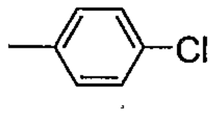
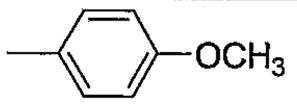
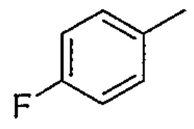
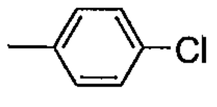
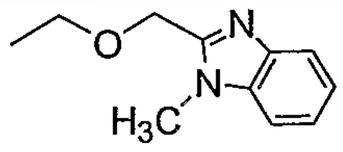
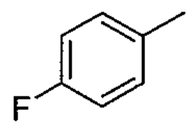
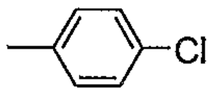
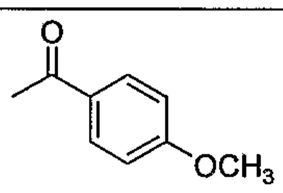
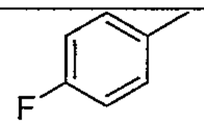
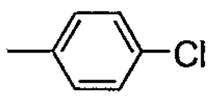
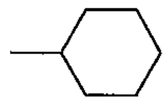
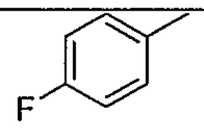
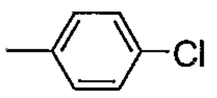
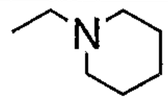
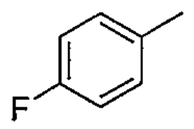
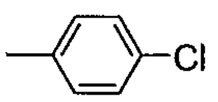
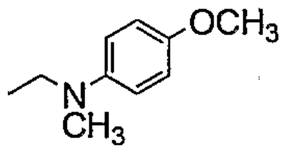
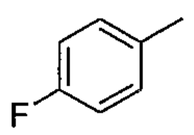
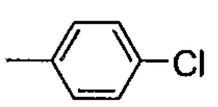
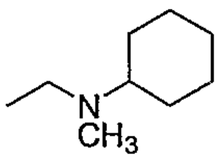
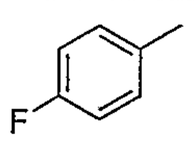
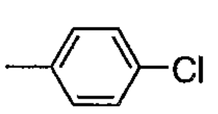
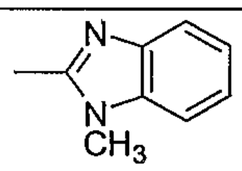
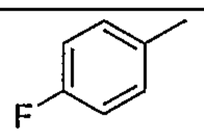
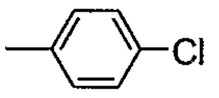
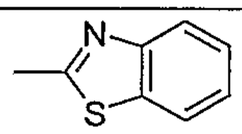
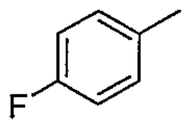
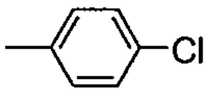
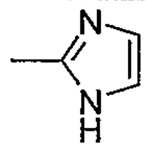
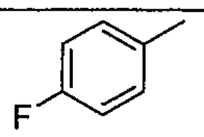
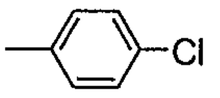
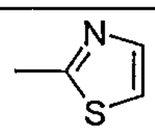
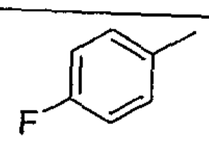
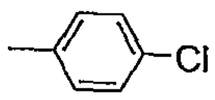
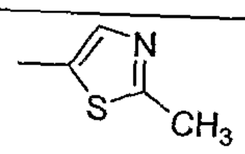
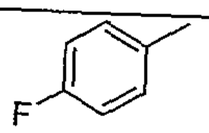
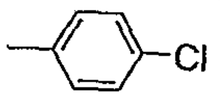
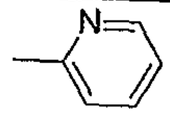
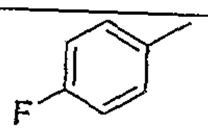
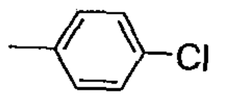
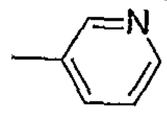
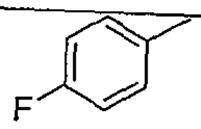
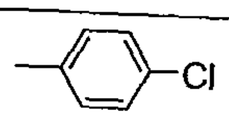
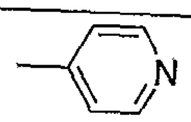
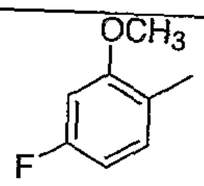
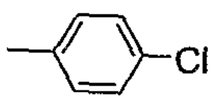
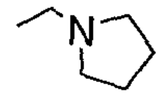
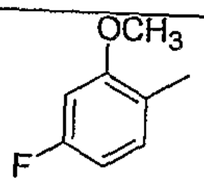
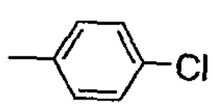
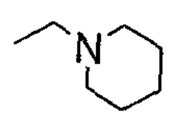
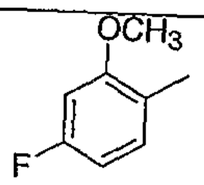
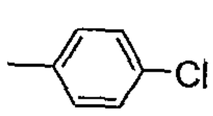
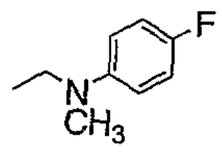
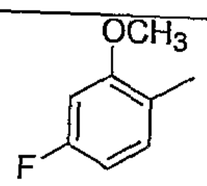
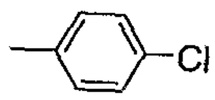
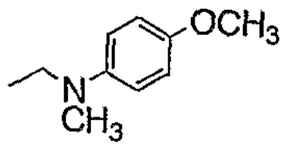
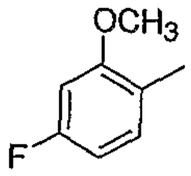
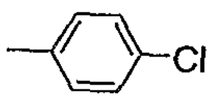
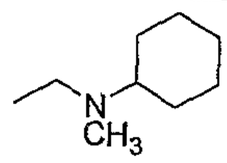
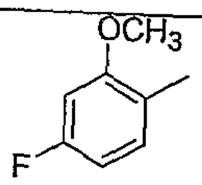
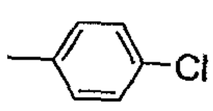
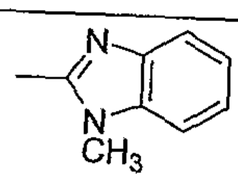
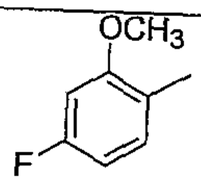
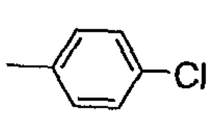
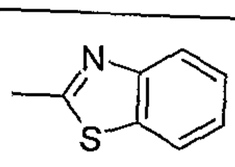
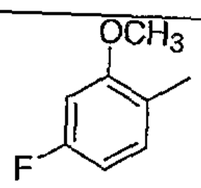
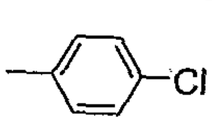
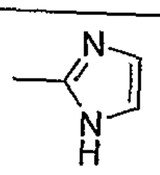
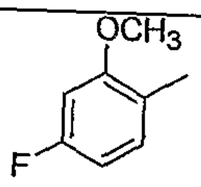
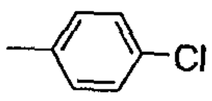
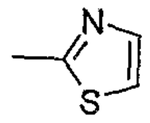
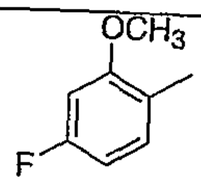
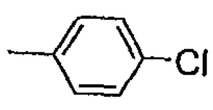
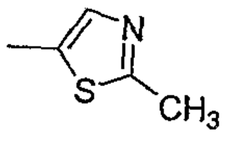
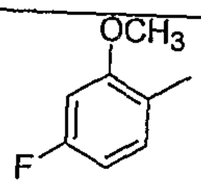
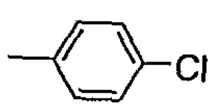
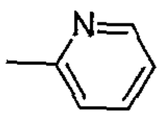
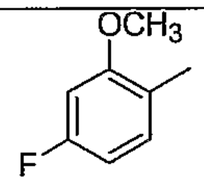
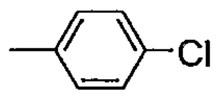
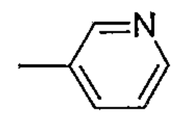
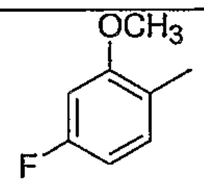
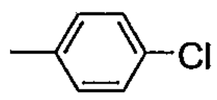
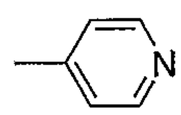
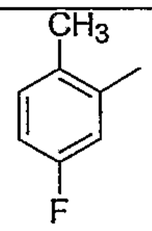
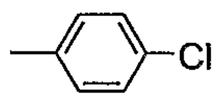
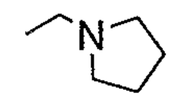
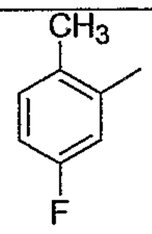
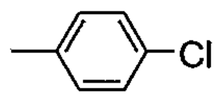
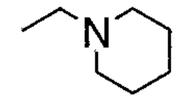
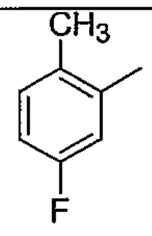
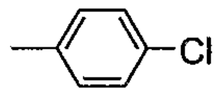
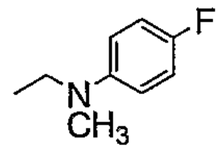
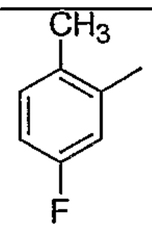
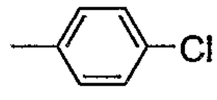
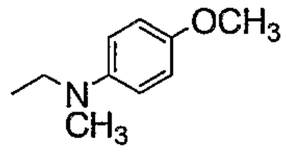
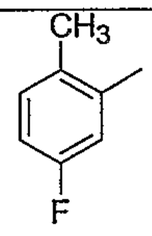
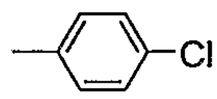
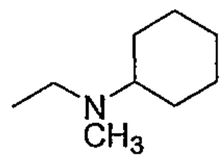
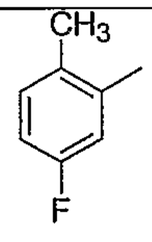
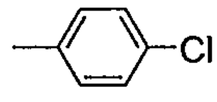
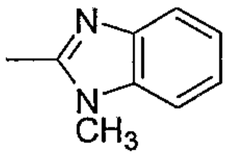
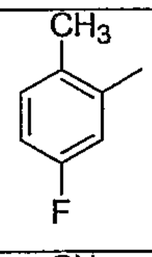
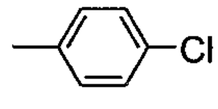
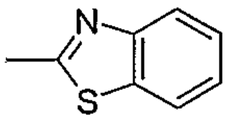
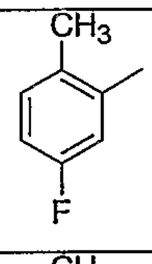
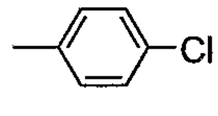
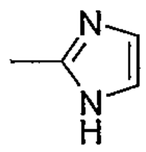
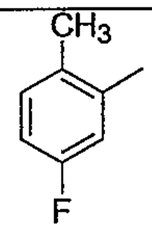
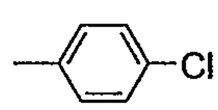
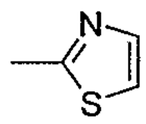
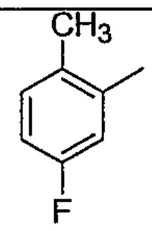
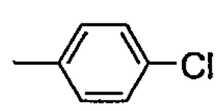
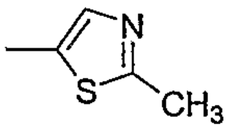
G-1			
G-2			
G-3			
G-4			
G-5			
G-6			
G-7			
G-8			
G-9			
G-10			

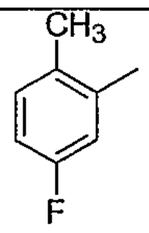
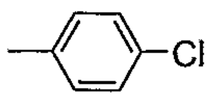
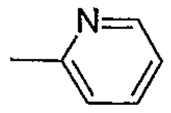
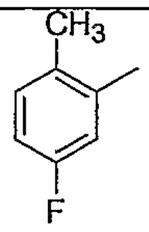
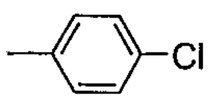
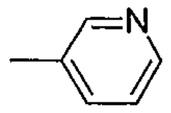
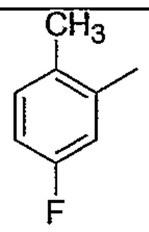
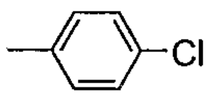
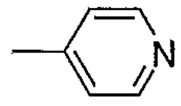
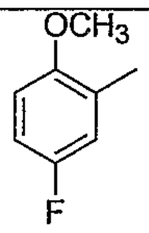
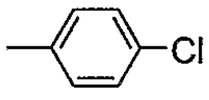
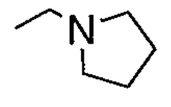
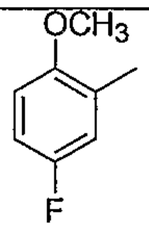
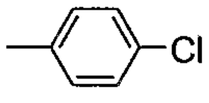
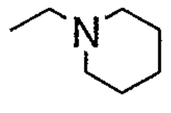
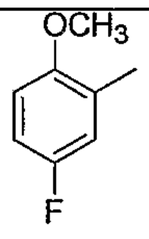
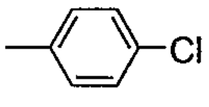
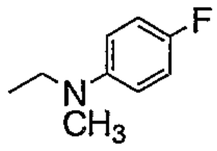
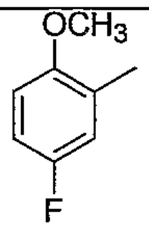
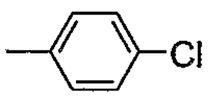
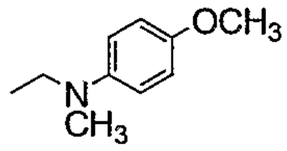
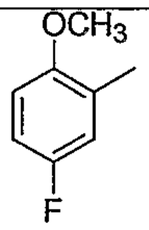
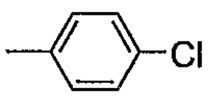
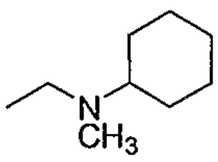
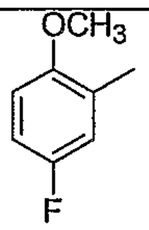
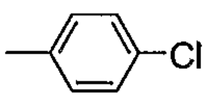
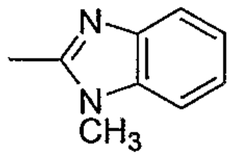
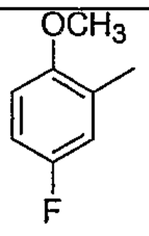
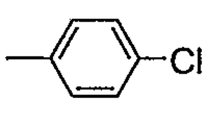
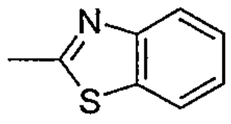
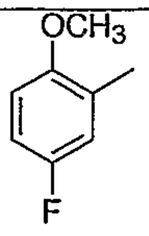
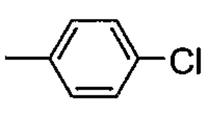
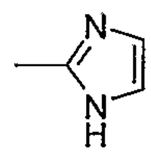
G-11			
G-12			
G-13			
G-14			
G-15			
G-16			
G-17			
G-18			
G-19			
G-20			
G-21			
G-22			
G-23			

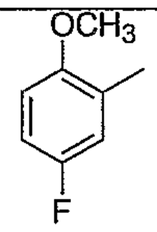
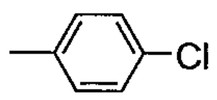
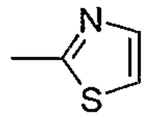
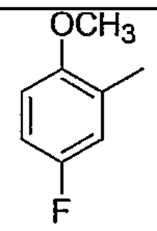
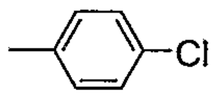
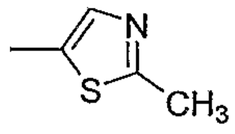
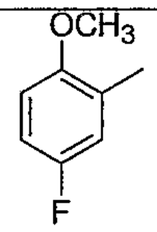
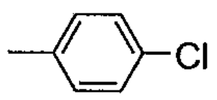
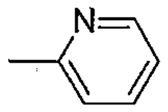
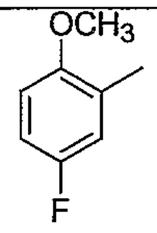
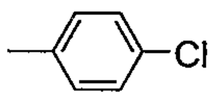
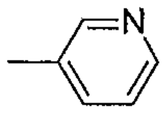
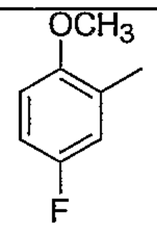
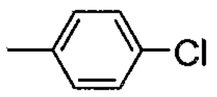
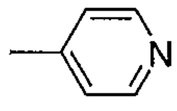
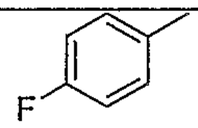
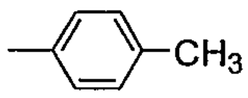
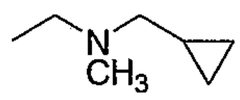
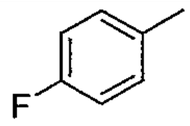
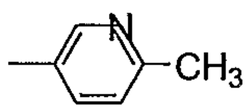
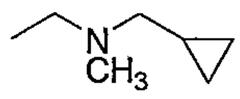
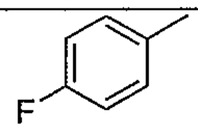
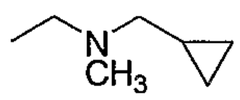
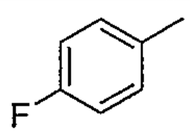
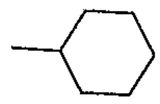
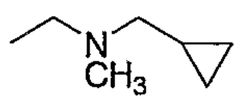
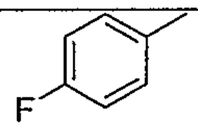
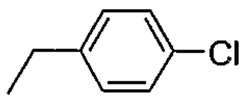
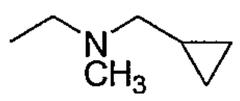
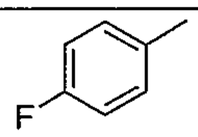
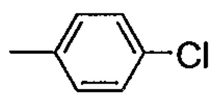
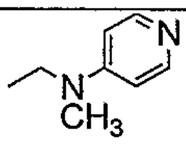
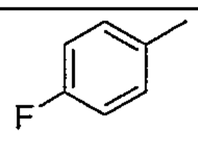
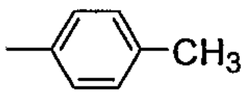
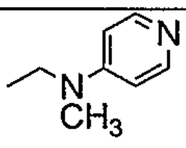
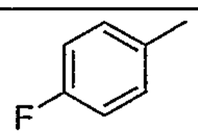
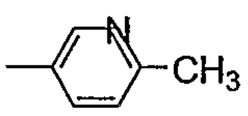
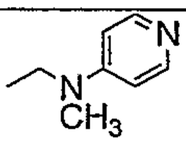
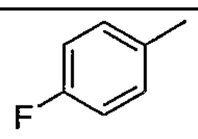
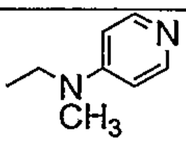
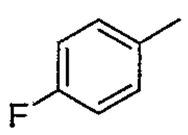
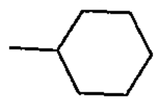
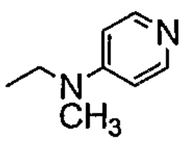
G-24			
G-25			
G-26			
G-27			
G-28			
G-29			
G-30			
G-31			
G-32			
G-33			
G-34			
G-35			
G-36			
G-37			
G-38			
G-39			
G-40			

G-41			
G-42			
G-43			
G-44			
G-45			
G-46			
G-47			
G-48			
G-49			
G-50			
G-51			
G-52			
G-53			
G-54			
G-55			

G-56			
G-57			
G-58			
G-59			
G-60			
G-61			
G-62			
G-63			
G-64			
G-65			
G-66			
G-67			
G-68			
G-69			
G-70			

G-71			
G-72			
G-73			
G-74			
G-75			
G-76			
G-77			
G-78			
G-79			
G-80			
G-81			
G-82			

G-83			
G-84			
G-85			
G-86			
G-87			
G-88			
G-89			
G-90			
G-91			
G-92			
G-93			

G-94			
G-95			
G-96			
G-97			
G-98			
G-99			
G-100			
G-101		CH_3	
G-102			
G-103			
G-104			
G-105			
G-106			
G-107		CH_3	
G-108			

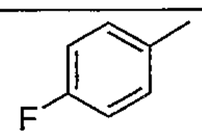
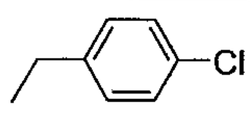
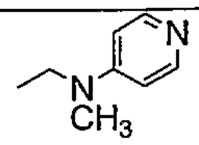
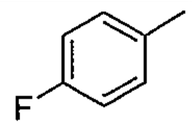
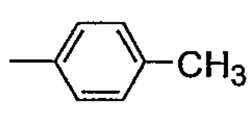
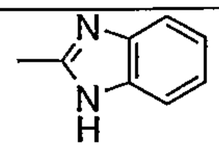
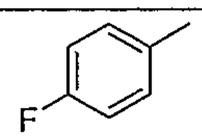
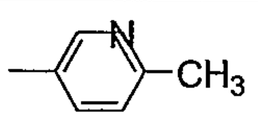
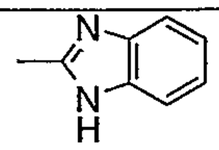
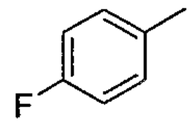
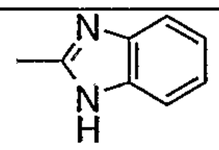
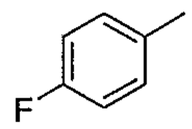
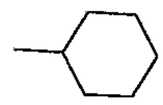
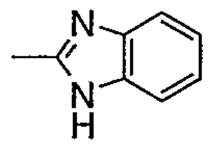
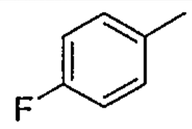
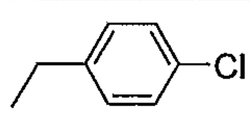
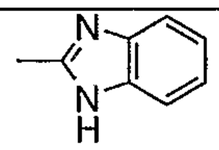
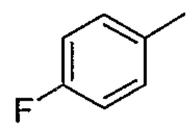
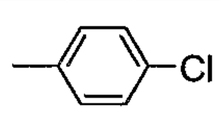
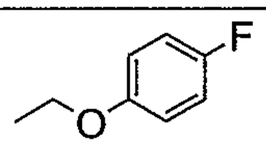
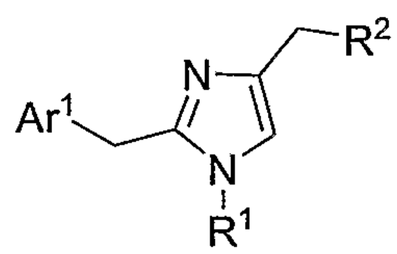
G-109			
G-110			
G-111			
G-112		CH_3	
G-113			
G-114			
G-115			

TABLE G-1B



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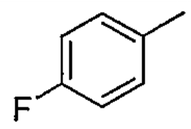
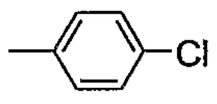
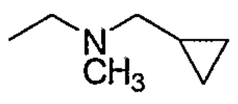
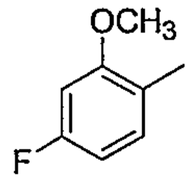
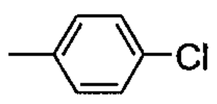
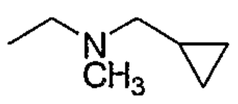
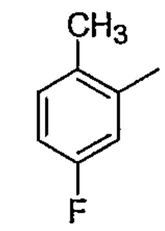
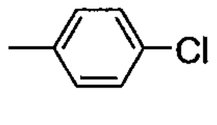
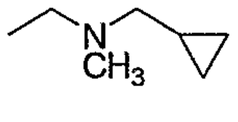
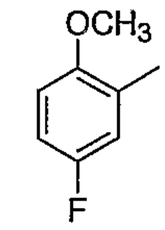
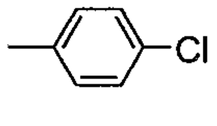
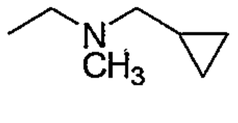
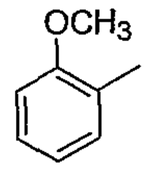
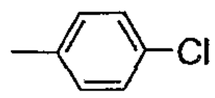
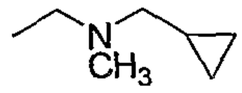
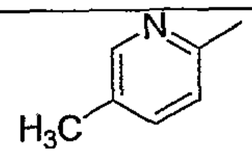
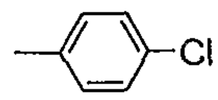
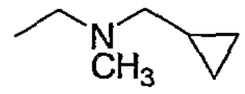
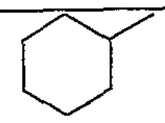
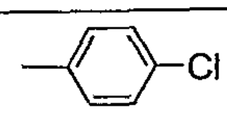
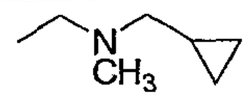
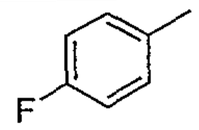
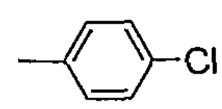
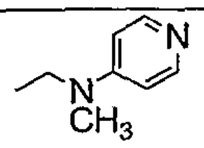
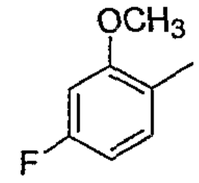
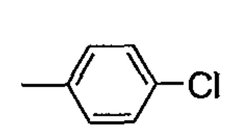
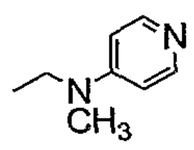
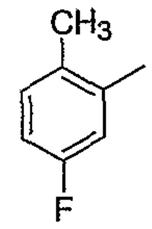
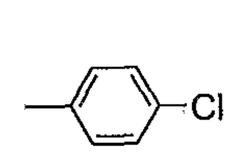
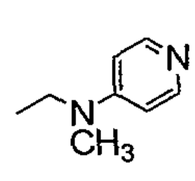
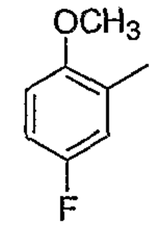
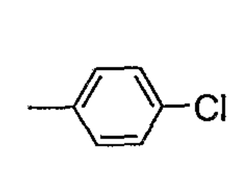
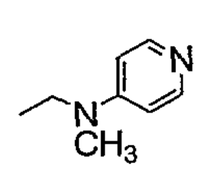
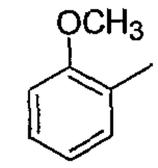
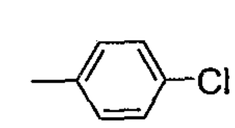
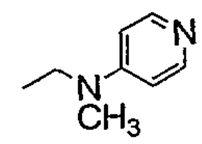
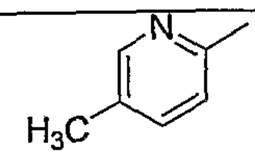
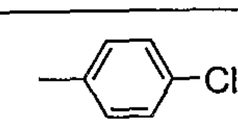
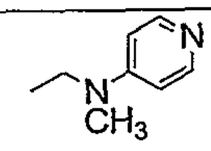
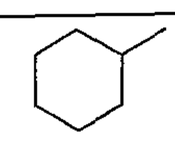
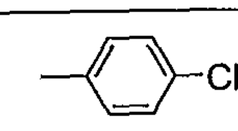
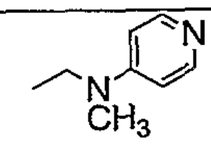
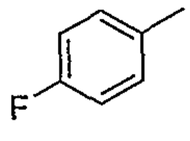
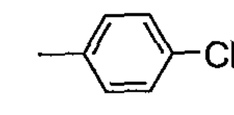
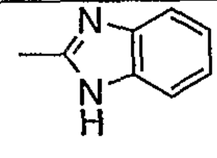
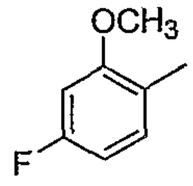
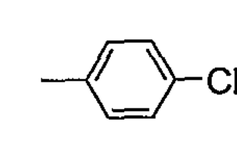
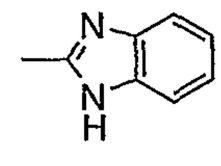
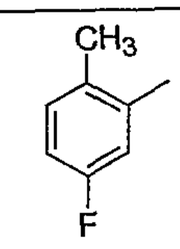
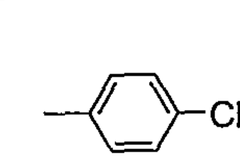
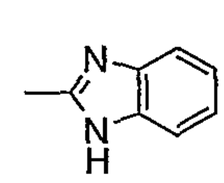
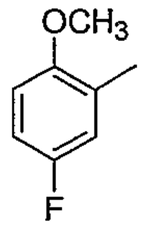
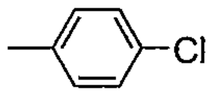
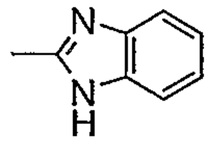
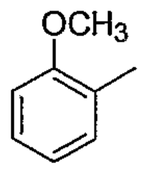
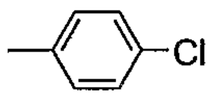
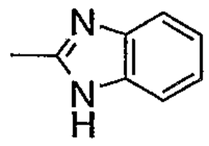
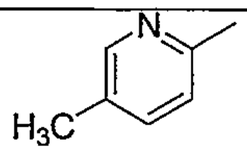
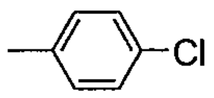
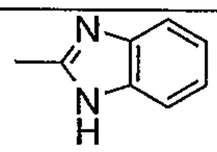
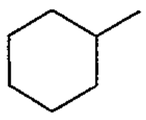
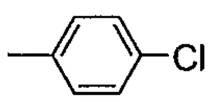
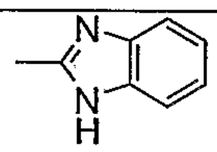
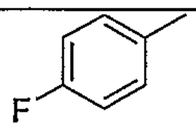
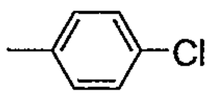
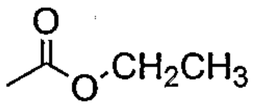
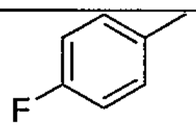
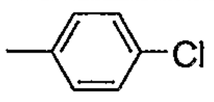
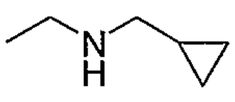
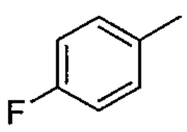
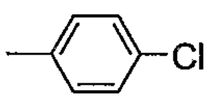
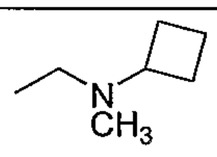
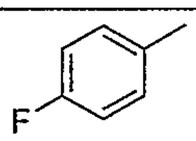
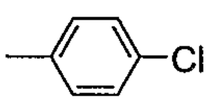
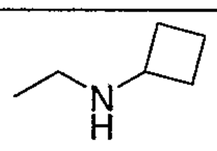
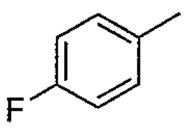
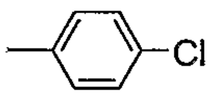
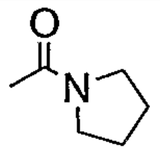
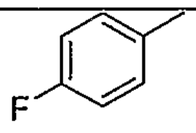
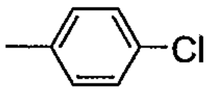
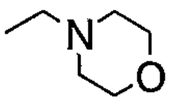
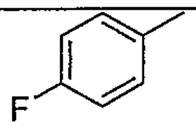
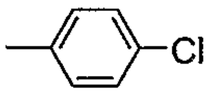
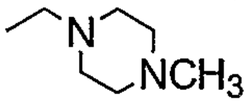
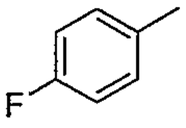
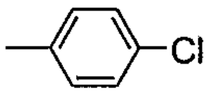
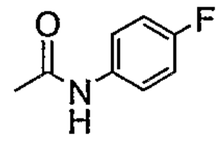
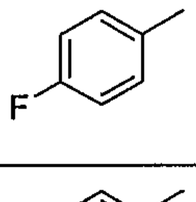
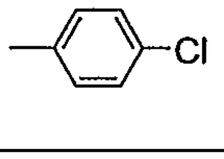
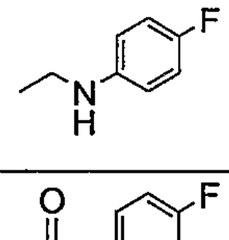
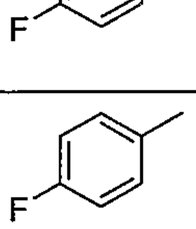
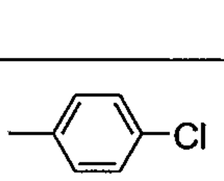
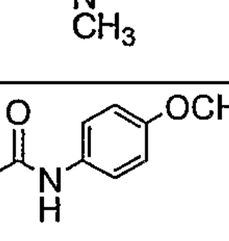
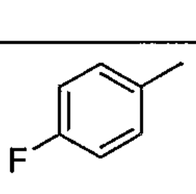
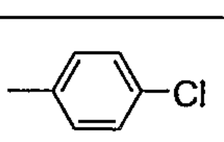
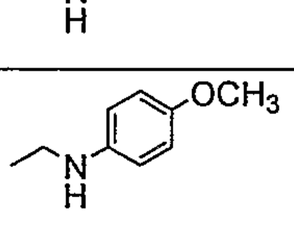
G-116			
G-117			
G-118			
G-119			

G-120			
G-121			
G-122			
G-123			
G-124			
G-125			
G-126			
G-127			
G-128			
G-129			
G-130			
G-131			
G-132			

G-133			
G-134			
G-135			
G-136			
G-137			
G-138			
G-139			
G-140			
G-141			
G-142			
G-143			
G-144			
G-145			
G-146			
G-147			
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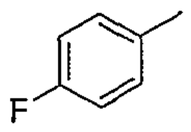
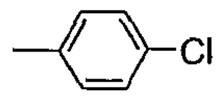
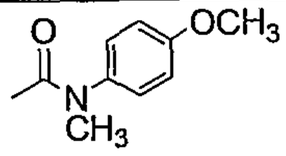
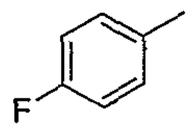
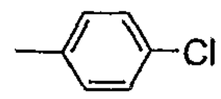
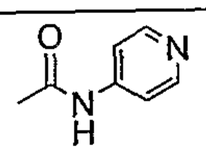
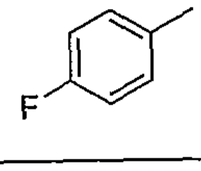
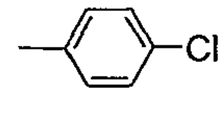
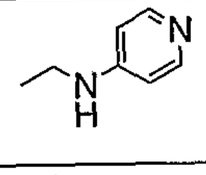
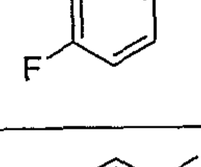
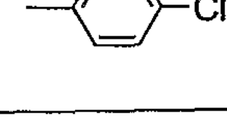
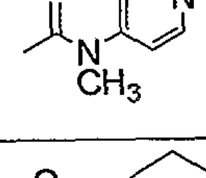
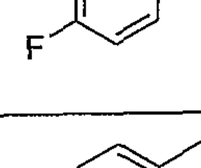
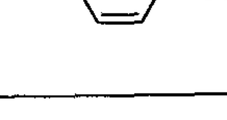
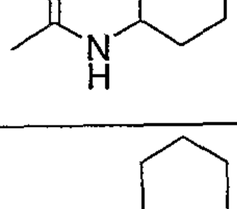
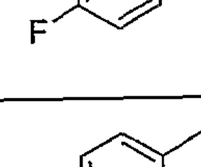
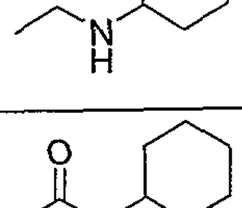
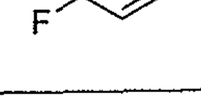
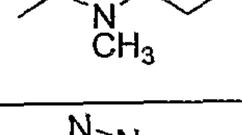
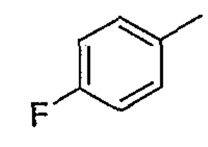
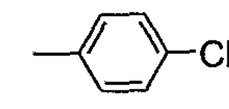
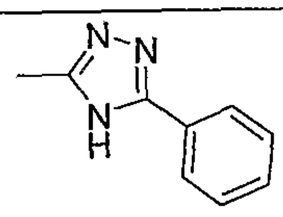
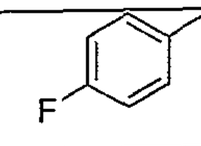
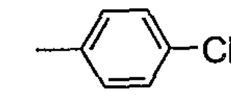
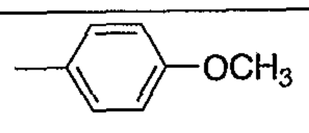
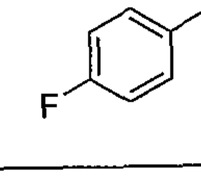
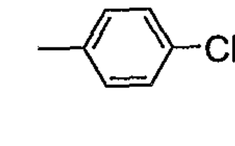
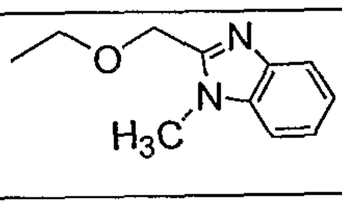
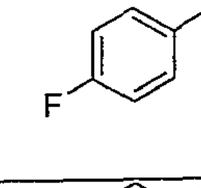
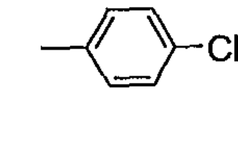
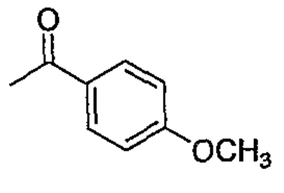
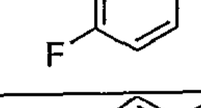
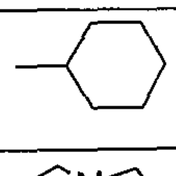
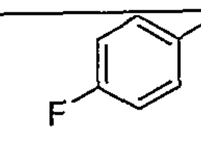
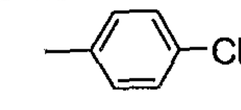
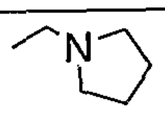
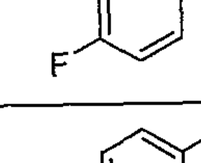
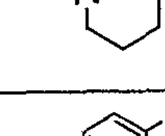
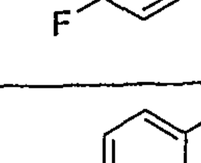
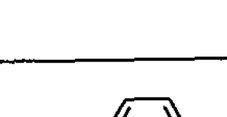
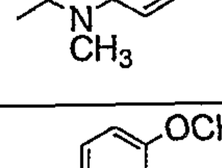
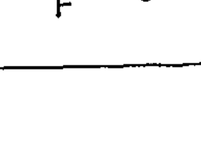
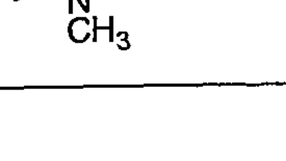
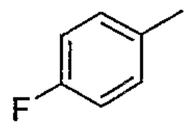
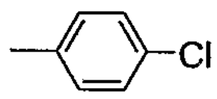
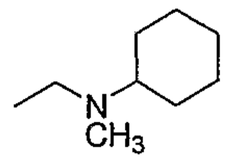
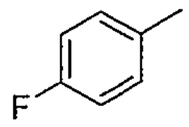
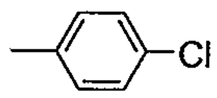
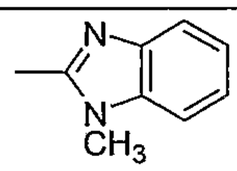
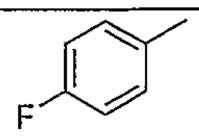
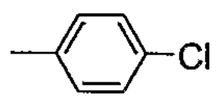
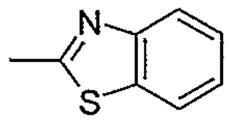
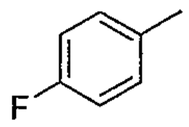
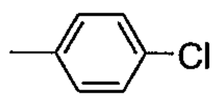
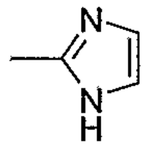
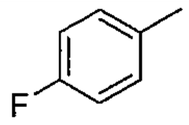
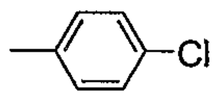
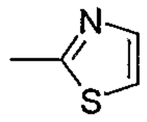
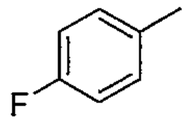
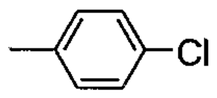
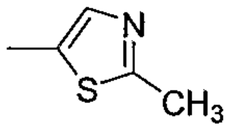
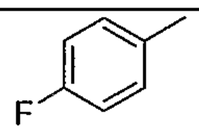
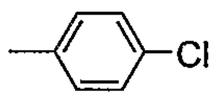
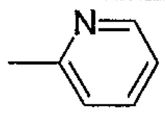
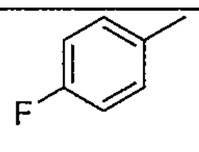
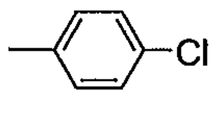
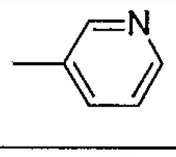
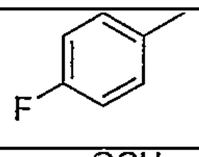
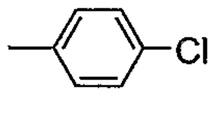
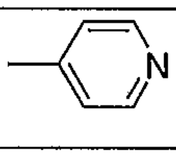
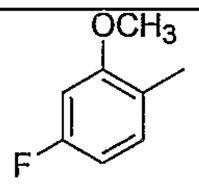
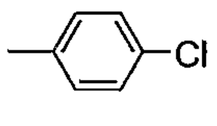
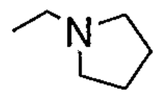
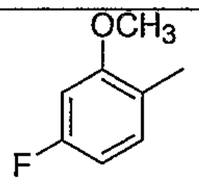
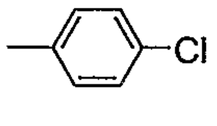
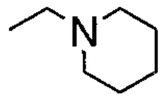
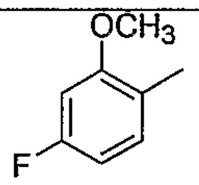
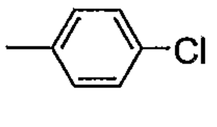
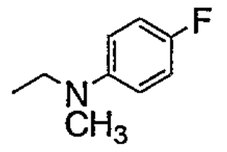
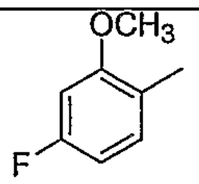
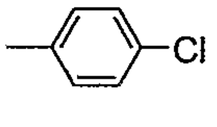
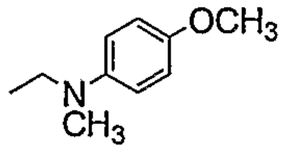
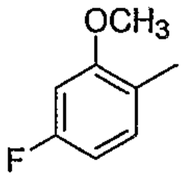
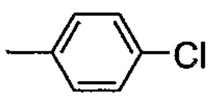
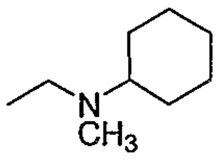
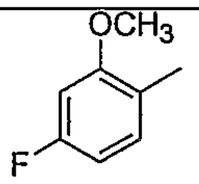
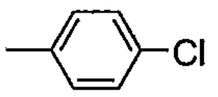
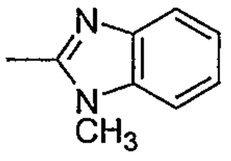
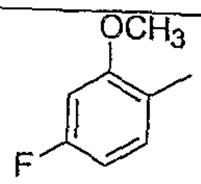
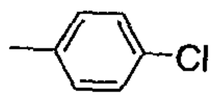
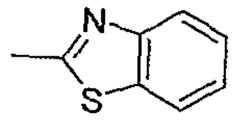
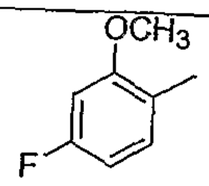
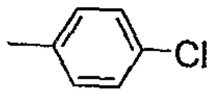
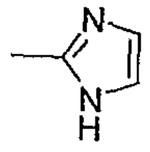
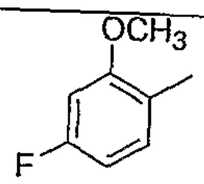
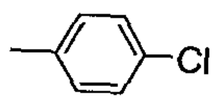
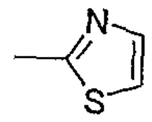
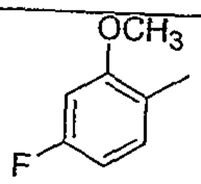
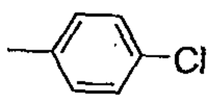
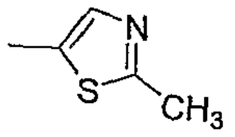
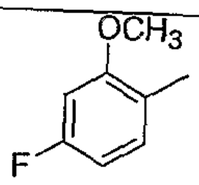
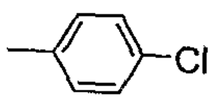
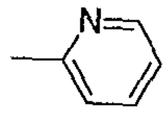
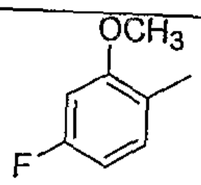
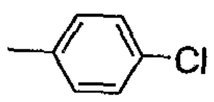
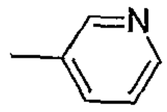
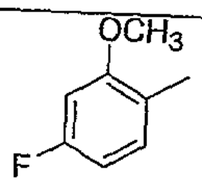
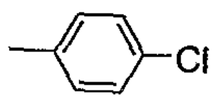
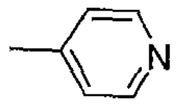
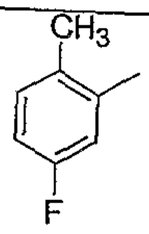
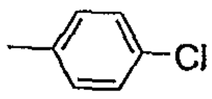
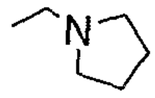
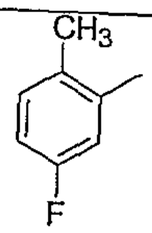
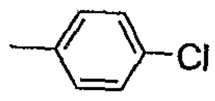
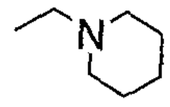
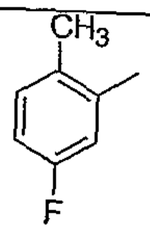
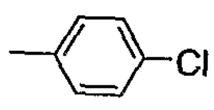
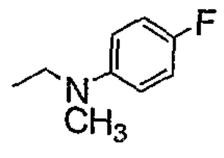
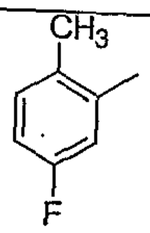
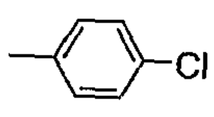
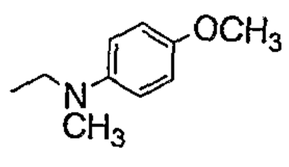
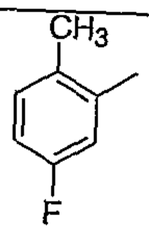
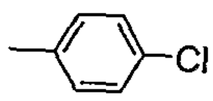
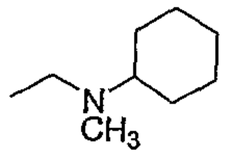
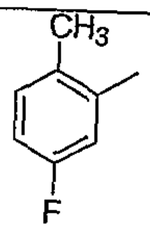
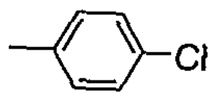
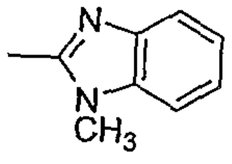
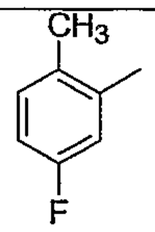
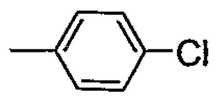
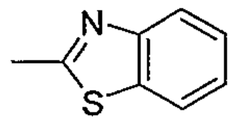
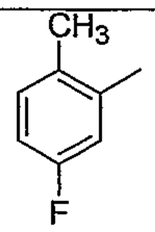
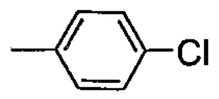
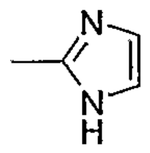
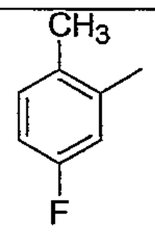
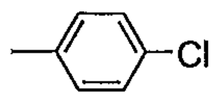
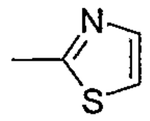
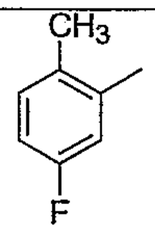
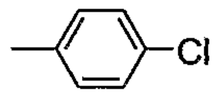
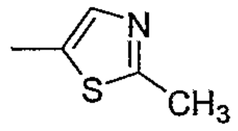
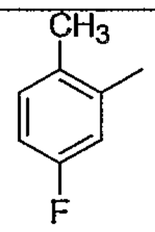
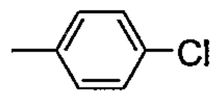
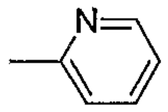
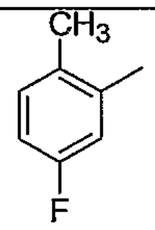
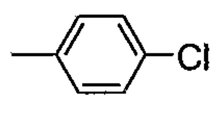
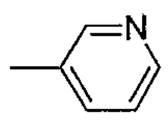
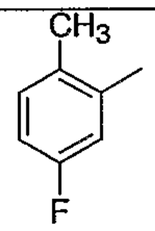
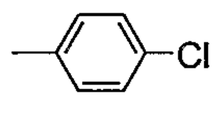
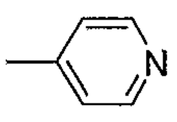
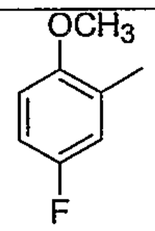
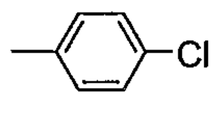
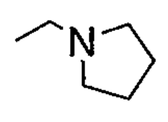
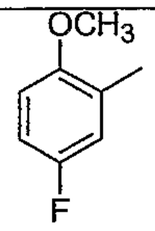
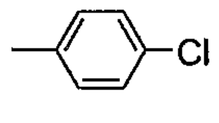
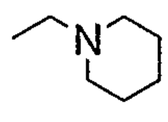
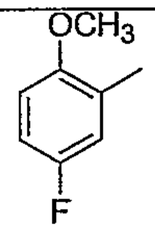
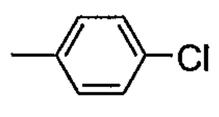
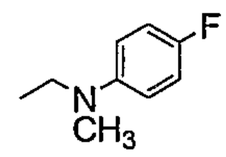
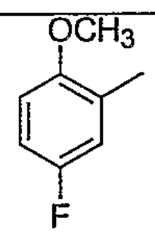
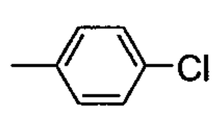
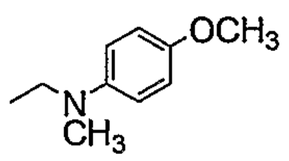
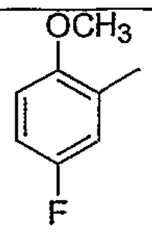
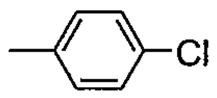
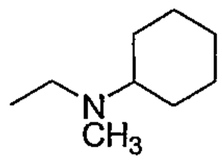
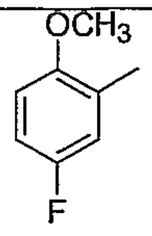
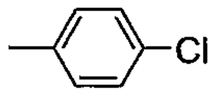
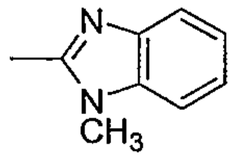
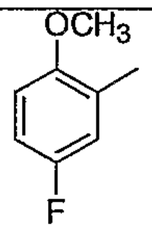
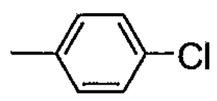
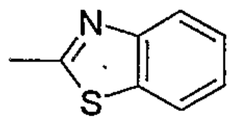
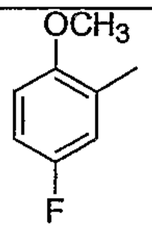
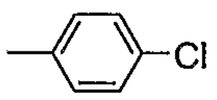
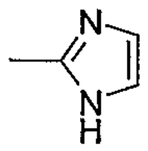
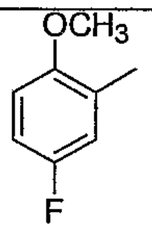
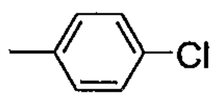
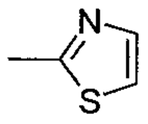
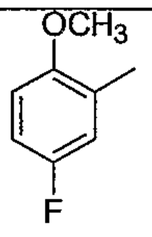
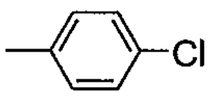
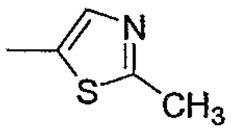
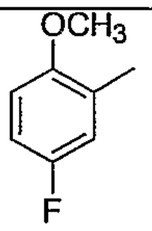
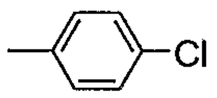
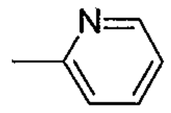
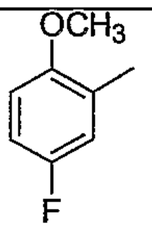
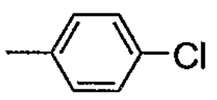
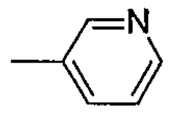
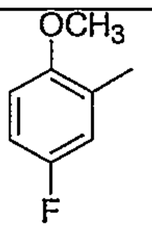
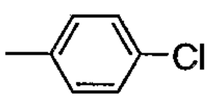
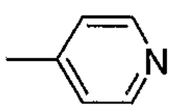
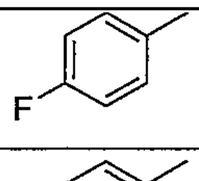
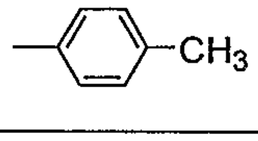
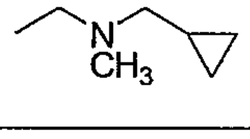
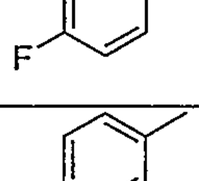
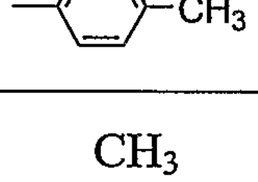
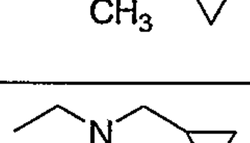
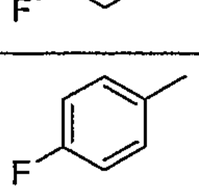
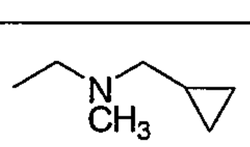
G-149			
G-150			
G-151			
G-152			
G-153			
G-154			
G-155			
G-156			
G-157			
G-158			
G-159			
G-160			
G-161			
G-162			
G-163			
G-164			

G-165			
G-166			
G-167			
G-168			
G-169			
G-170			
G-171			
G-172			
G-173			
G-174			
G-175			
G-176			
G-177			
G-178			
G-179			

G-180			
G-181			
G-182			
G-183			
G-184			
G-185			
G-186			
G-187			
G-188			
G-189			
G-190			
G-191			
G-192			

G-193			
G-194			
G-195			
G-196			
G-197			
G-198			
G-199			
G-200			
G-201			
G-202			
G-203			

G-204			
G-205			
G-206			
G-207			
G-208			
G-209			
G-210			
G-211			
G-212			
G-213			
G-214			
G-215		CH_3	
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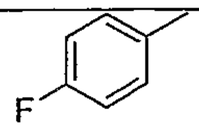
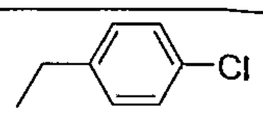
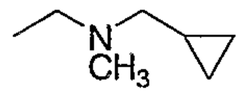
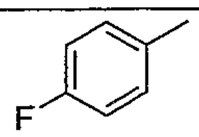
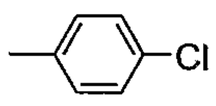
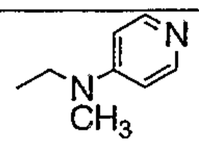
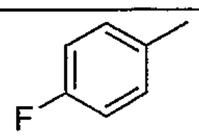
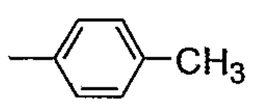
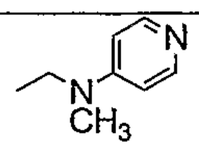
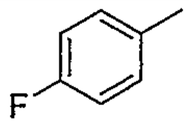
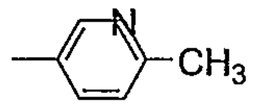
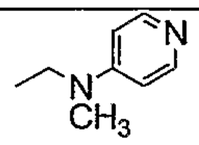
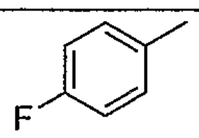
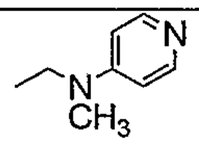
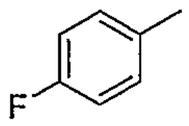
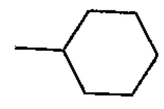
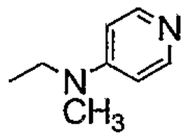
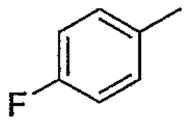
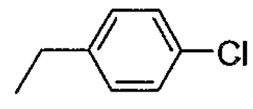
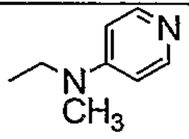
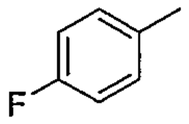
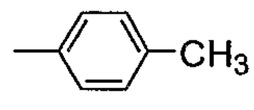
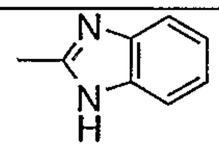
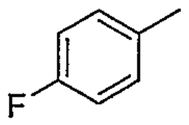
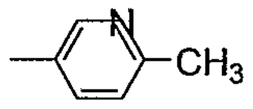
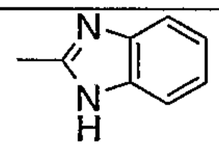
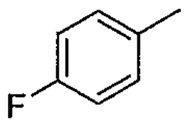
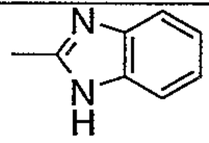
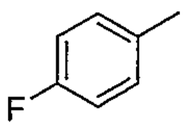
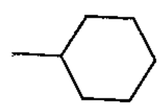
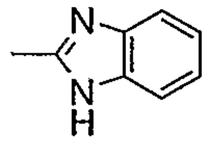
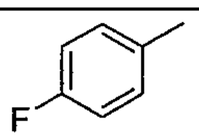
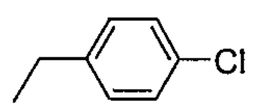
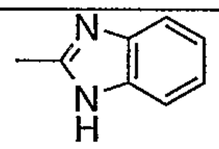
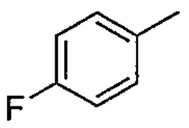
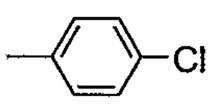
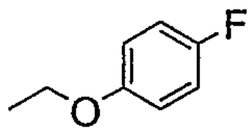
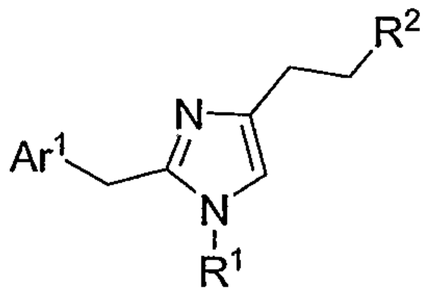
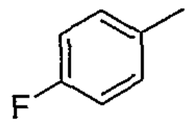
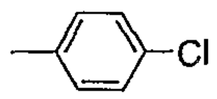
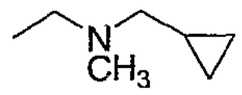
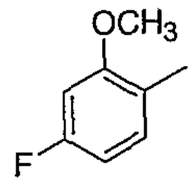
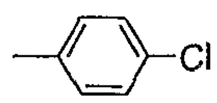
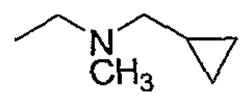
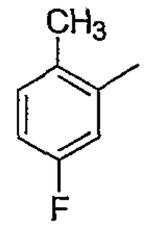
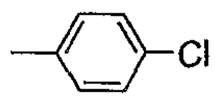
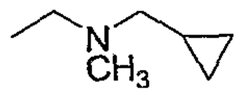
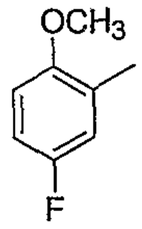
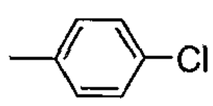
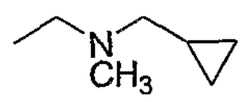
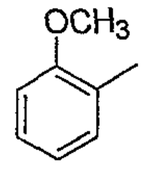
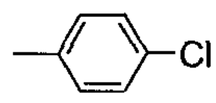
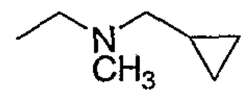
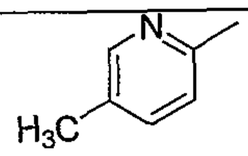
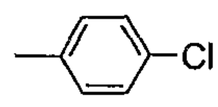
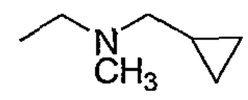
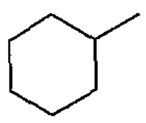
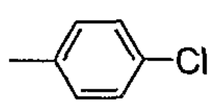
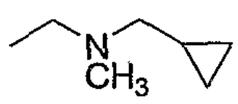
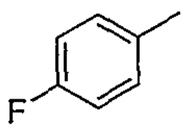
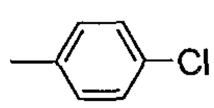
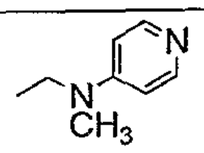
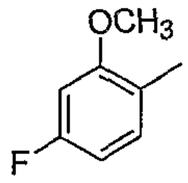
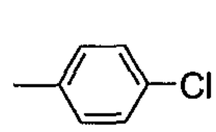
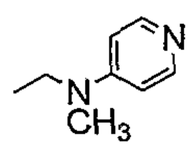
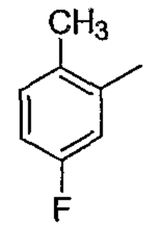
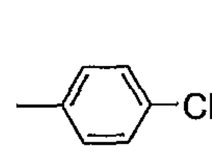
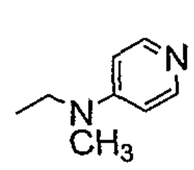
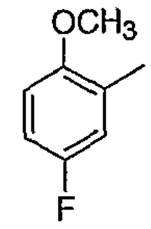
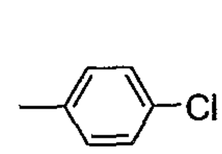
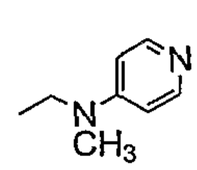
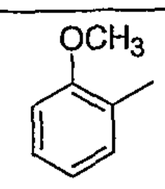
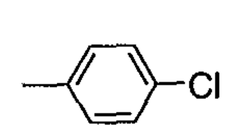
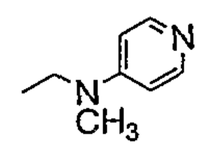
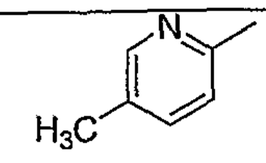
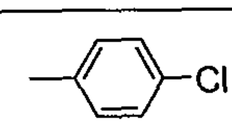
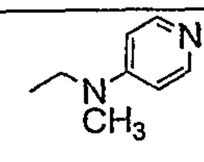
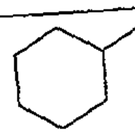
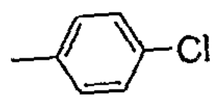
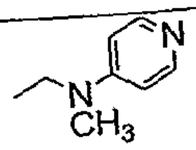
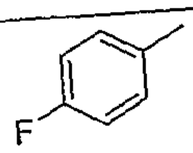
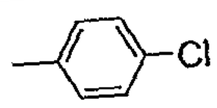
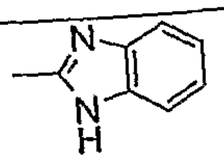
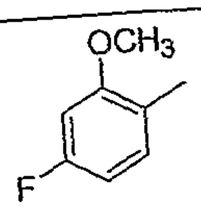
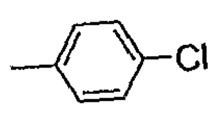
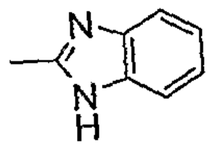
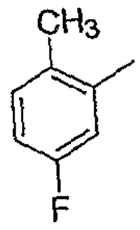
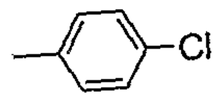
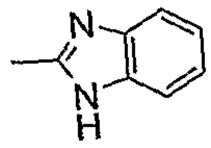
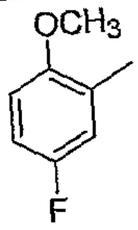
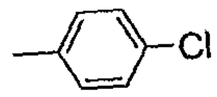
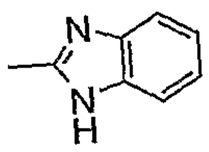
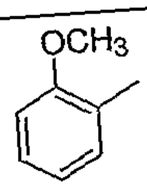
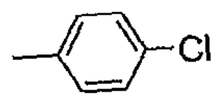
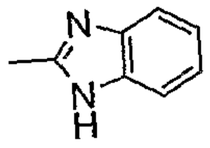
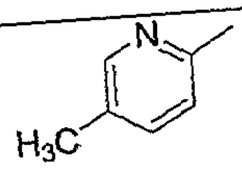
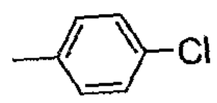
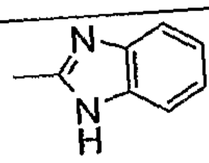
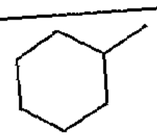
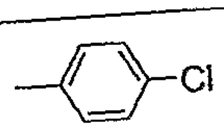
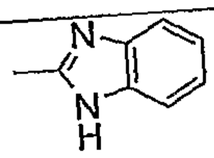
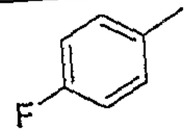
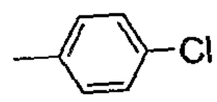
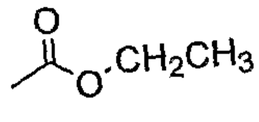
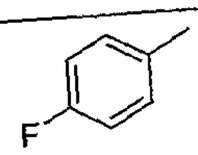
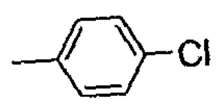
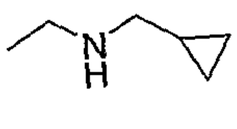
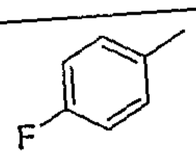
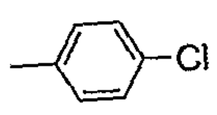
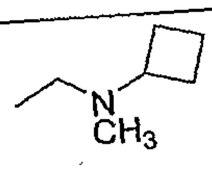
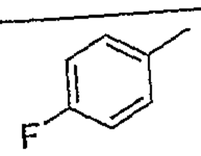
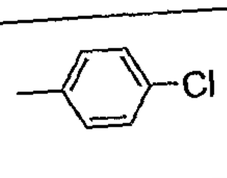
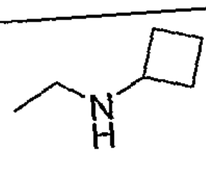
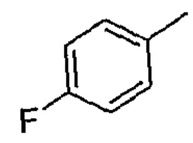
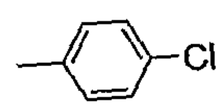
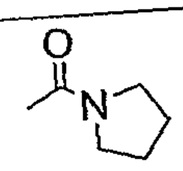
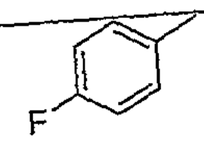
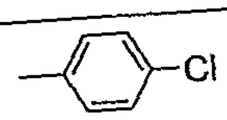
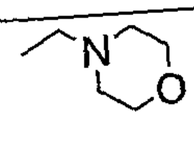
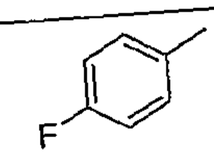
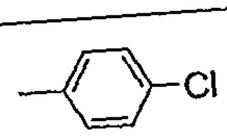
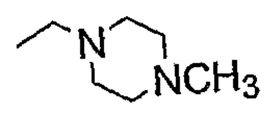
G-217			
G-218			
G-219			
G-220			
G-221		CH_3	
G-222			
G-223			
G-224			
G-225			
G-226		CH_3	
G-227			
G-228			
G229			

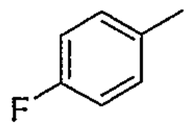
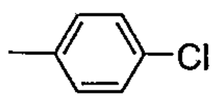
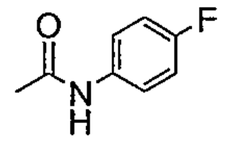
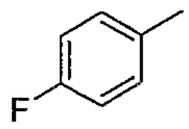
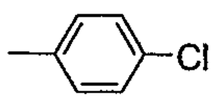
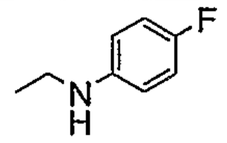
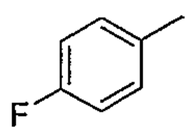
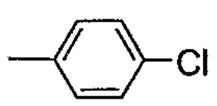
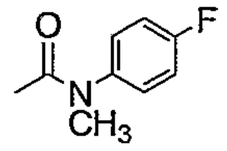
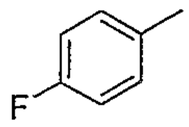
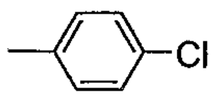
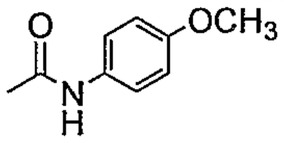
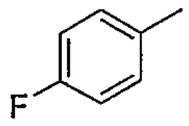
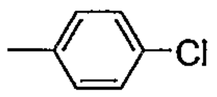
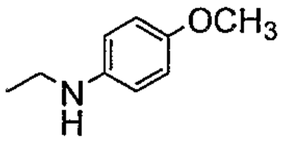
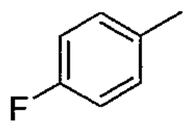
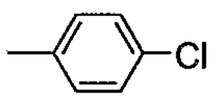
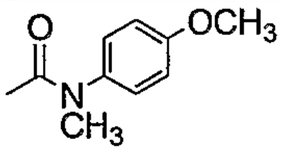
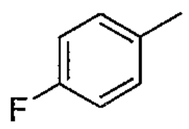
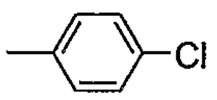
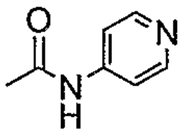
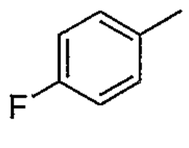
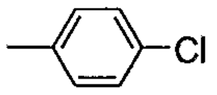
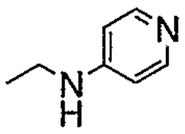
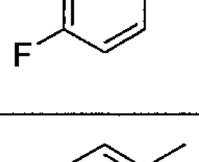
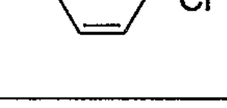
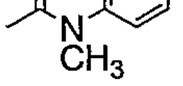
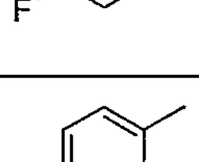
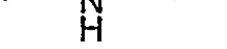
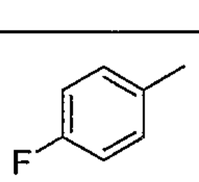
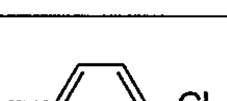
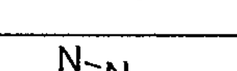
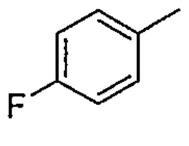
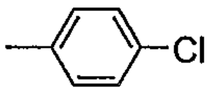
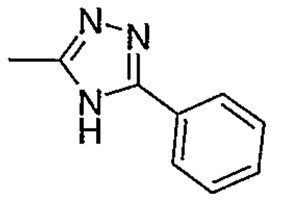
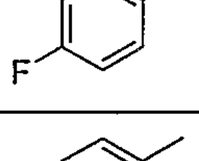
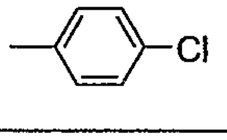
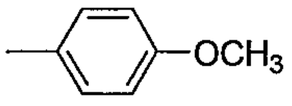
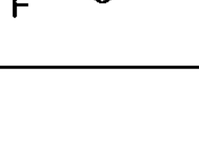
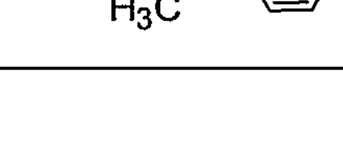
TABLE G-1C

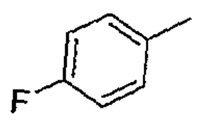
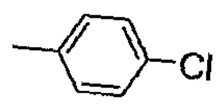
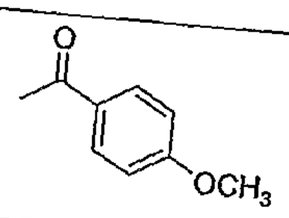
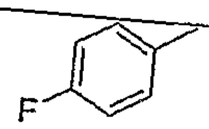
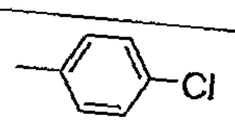
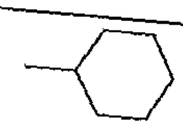
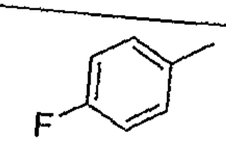
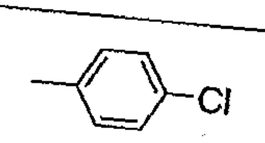
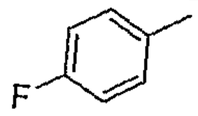
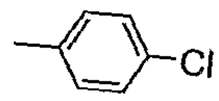
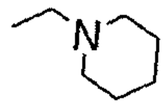
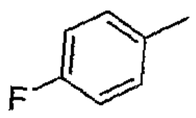
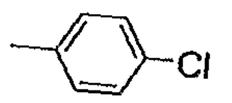
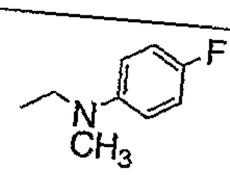
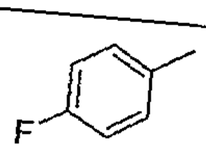
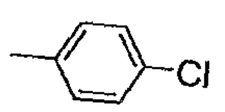
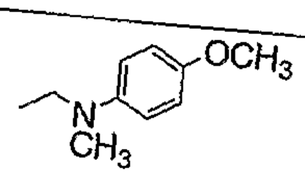
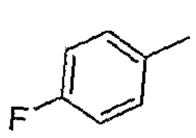
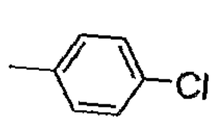
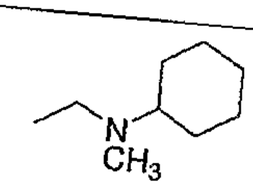
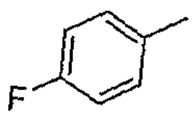
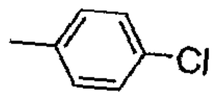
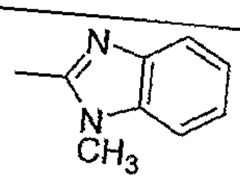
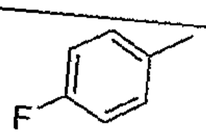
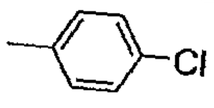
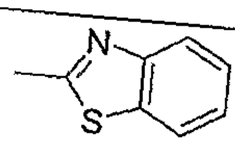
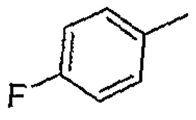
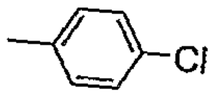
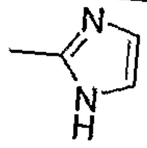
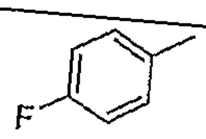
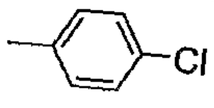
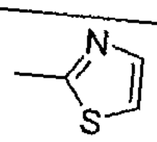
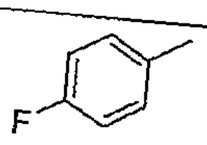
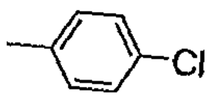
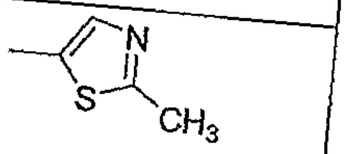
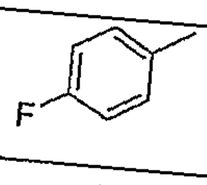
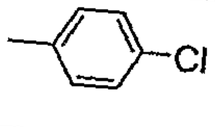
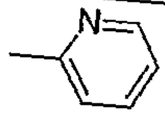
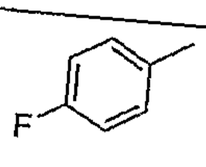
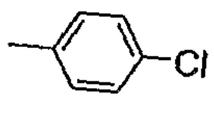
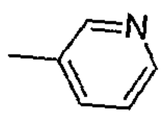
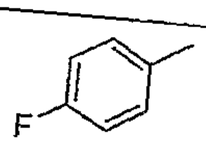
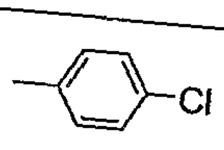
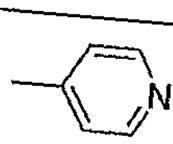
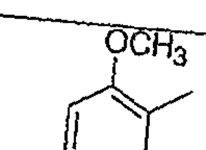
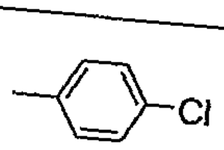
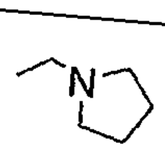


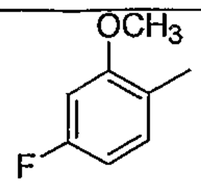
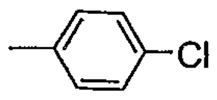
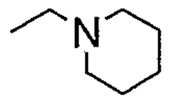
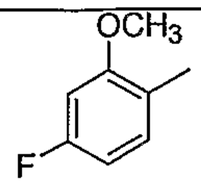
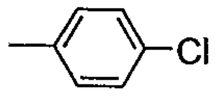
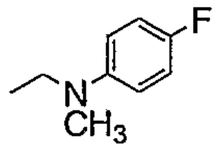
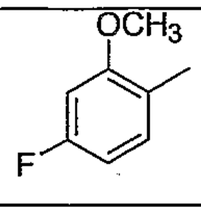
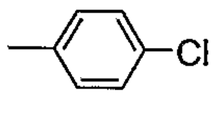
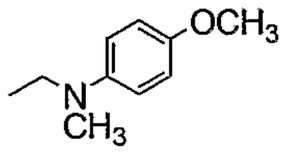
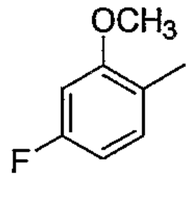
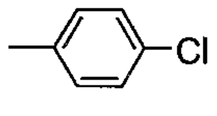
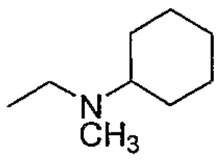
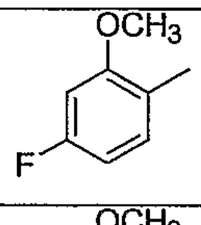
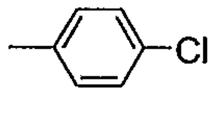
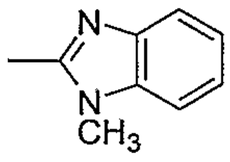
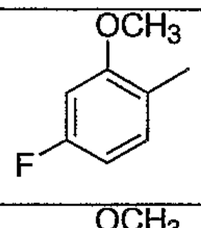
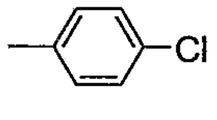
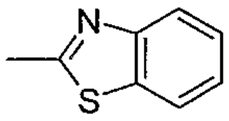
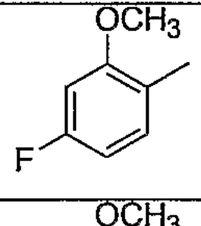
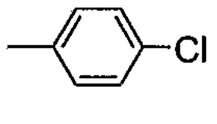
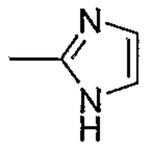
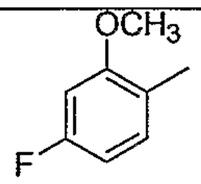
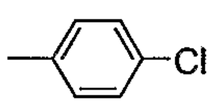
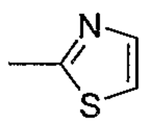
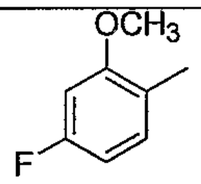
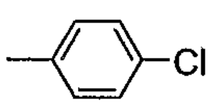
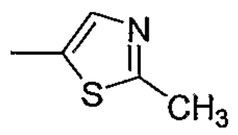
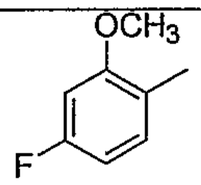
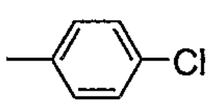
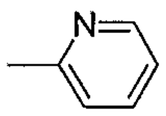
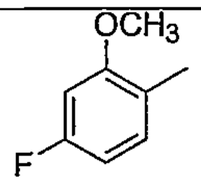
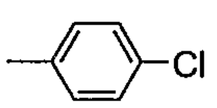
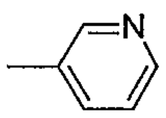
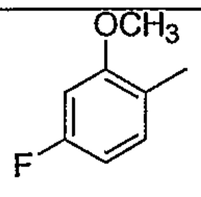
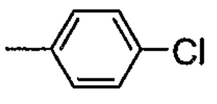
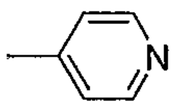
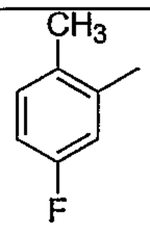
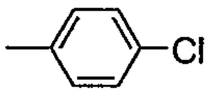
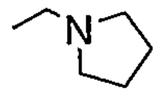
Cpd No.	Ar^1	R^1	R^2

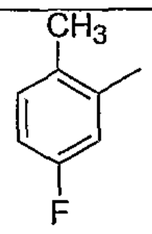
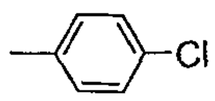
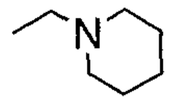
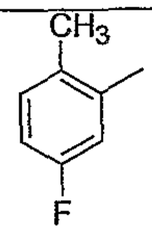
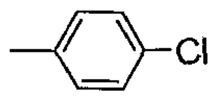
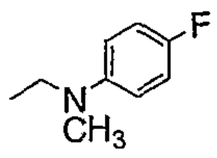
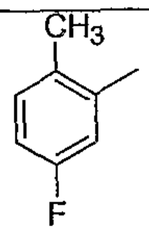
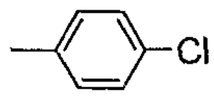
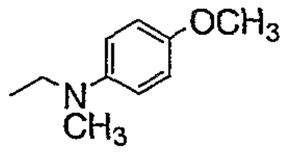
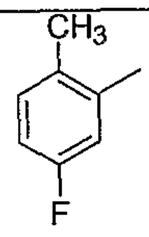
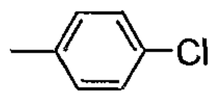
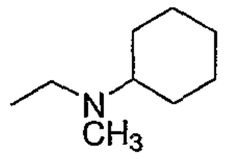
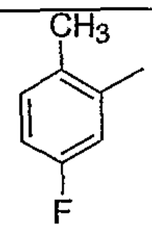
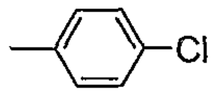
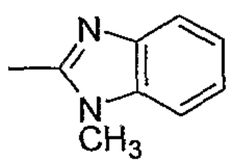
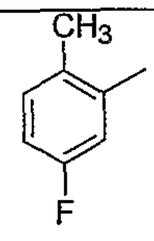
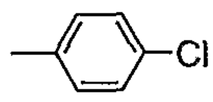
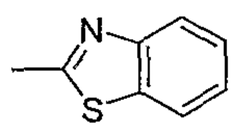
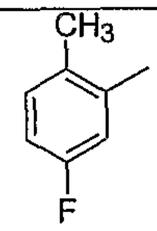
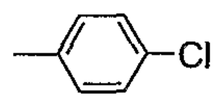
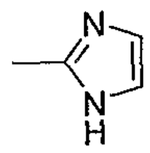
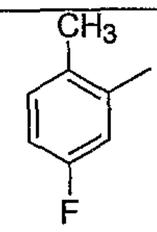
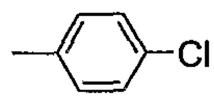
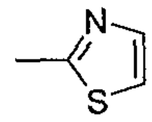
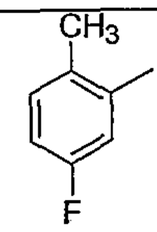
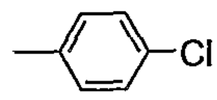
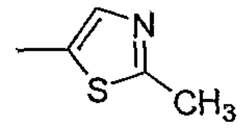
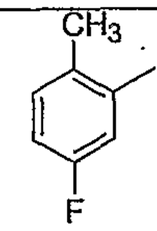
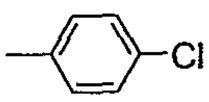
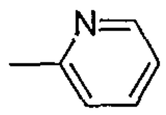
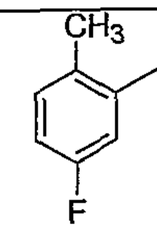
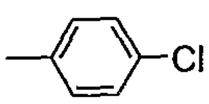
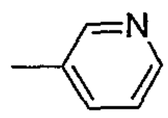
G-230			
G-231			
G-232			
G-233			
G-234			
G-235			
G-236			
G-237			
G-238			
G-239			
G-240			
G-241			
G-242			

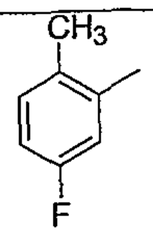
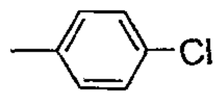
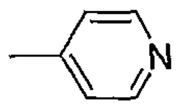
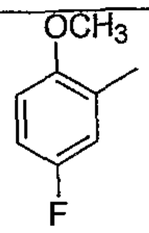
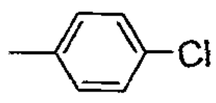
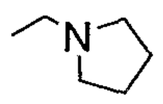
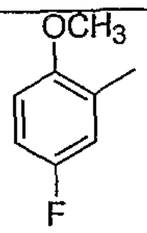
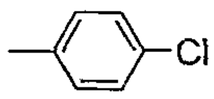
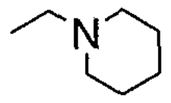
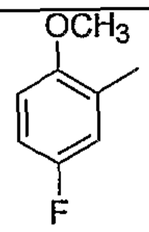
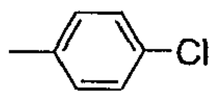
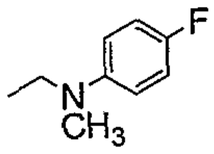
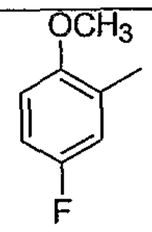
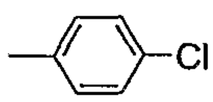
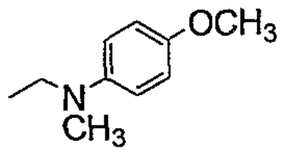
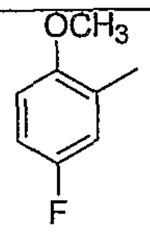
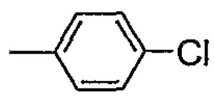
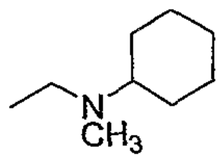
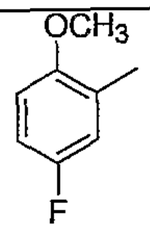
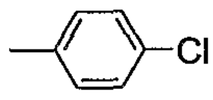
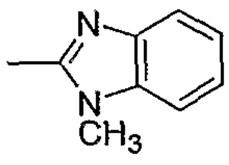
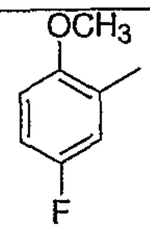
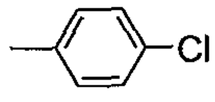
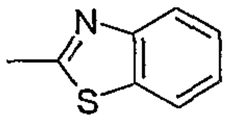
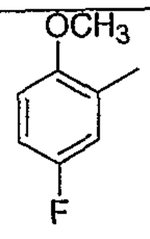
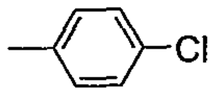
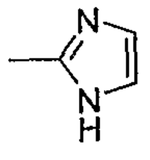
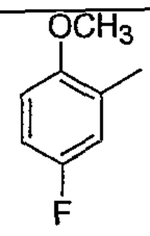
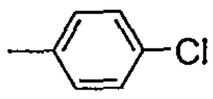
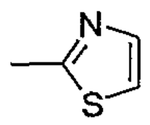
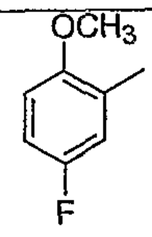
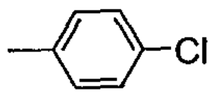
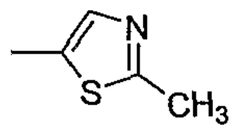
G-243			
G-244			
G-245			
G-246			
G-247			
G-248			
G-249			
G-250			
G-251			
G-252			
G-253			
G-254			
G-255			
G-256			
G-257			

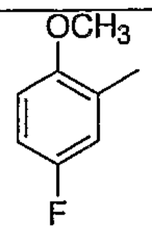
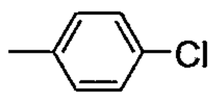
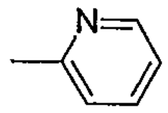
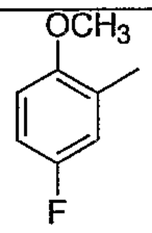
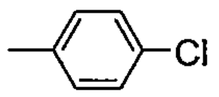
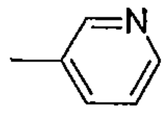
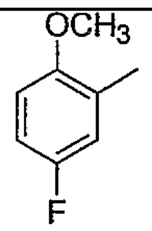
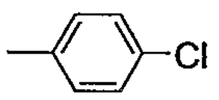
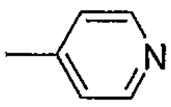
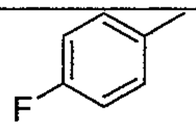
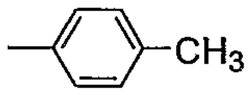
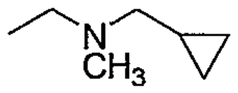
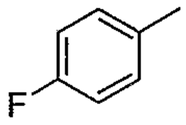
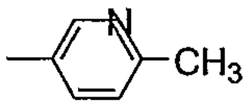
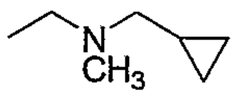
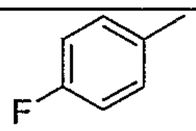
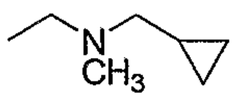
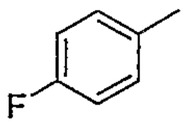
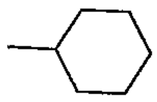
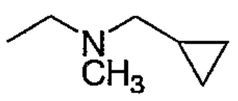
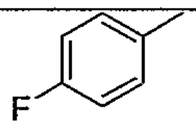
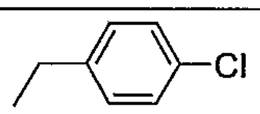
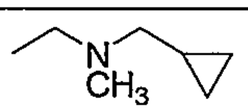
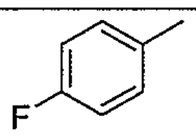
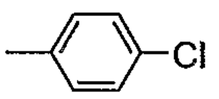
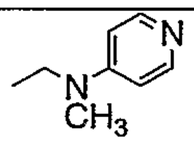
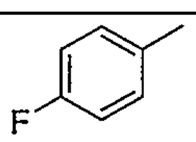
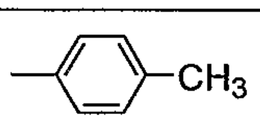
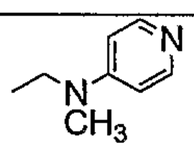
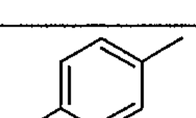
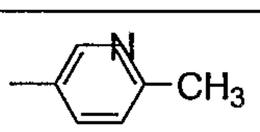
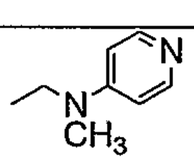
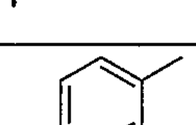
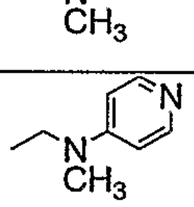
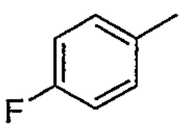
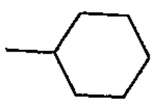
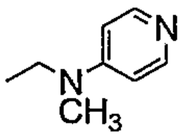
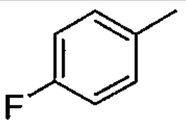
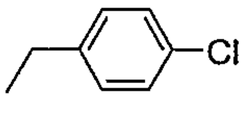
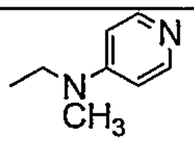
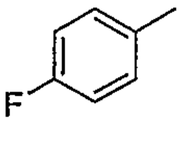
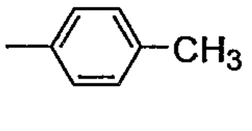
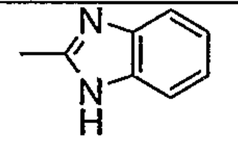
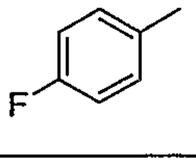
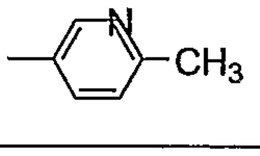
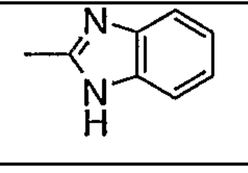
G-258			
G-259			
G-260			
G-261			
G-262			
G-263			
G-264			
G-265			
G-266			
G-267			
G-268			
G-269			
G-270			
G-271			
G-272			

G-273			
G-274			
G-275			
G-276			
G-277			
G-278			
G-279			
G-280			
G-281			
G-282			
G-283			
G-284			
G-285			
G-286			
G-287			
G-288			

G-289			
G-290			
G-291			
G-292			
G-293			
G-294			
G-295			
G-296			
G-297			
G-298			
G-299			
G-300			
G-301			

G-302			
G-303			
G-304			
G-305			
G-306			
G-307			
G-308			
G-309			
G-310			
G-311			
G-312			

G-313			
G-314			
G-315			
G-316			
G-317			
G-318			
G-319			
G-320			
G-321			
G-322			
G-323			

G-324			
G-325			
G-326			
G-327			
G-328			
G-329		CH_3	
G-330			
G-331			
G-332			
G-333			
G-334			
G-335		CH_3	
G-336			
G-337			
G-338			
G-339			

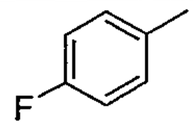
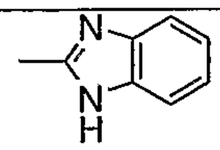
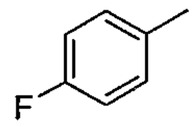
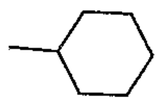
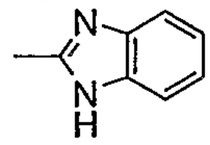
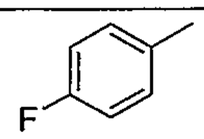
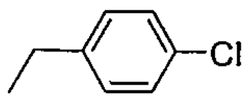
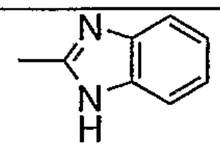
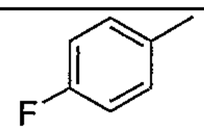
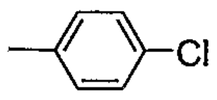
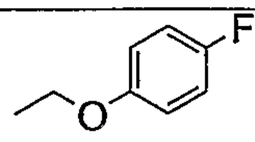
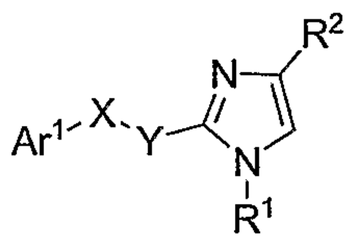
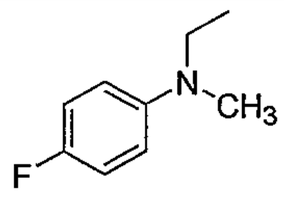
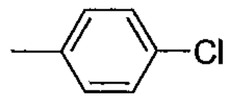
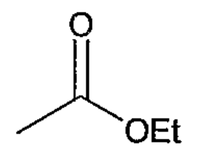
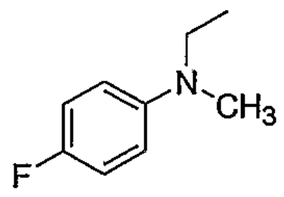
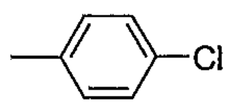
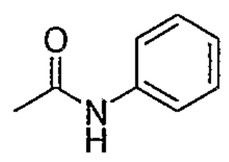
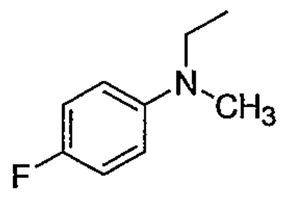
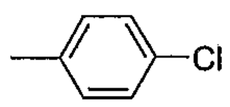
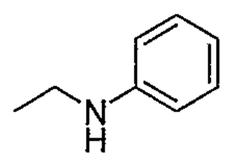
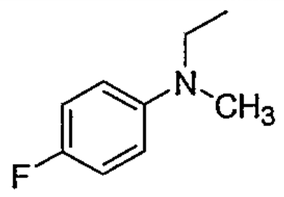
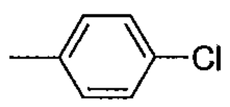
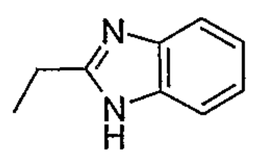
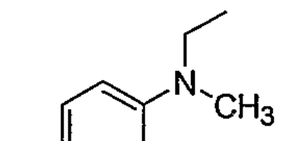
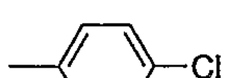
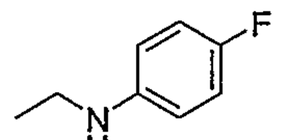
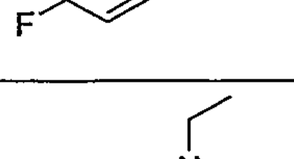
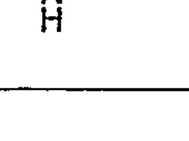
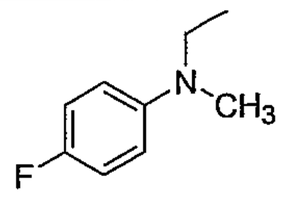
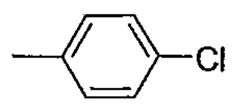
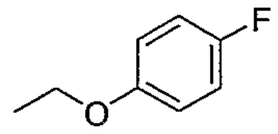
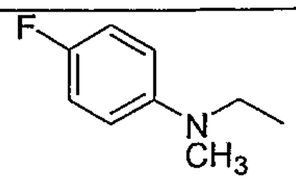
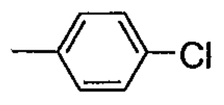
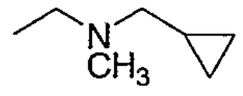
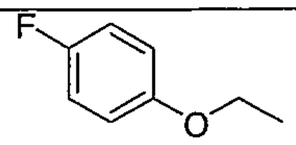
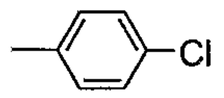
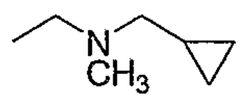
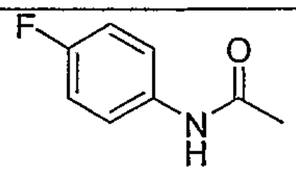
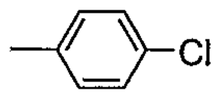
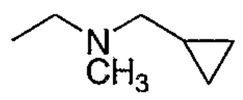
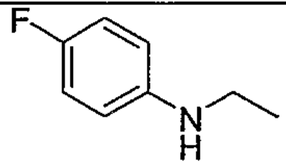
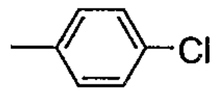
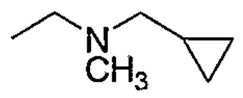
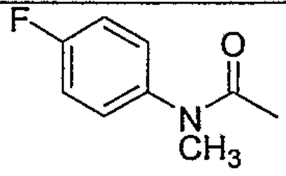
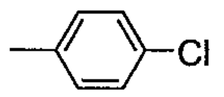
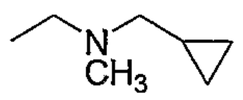
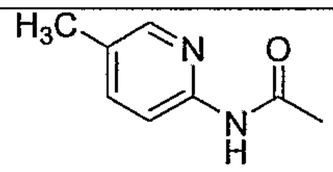
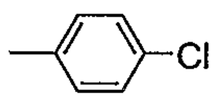
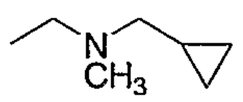
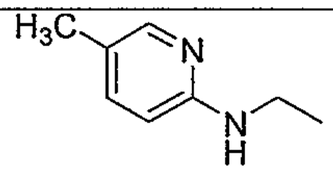
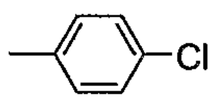
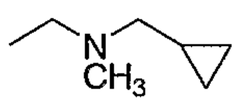
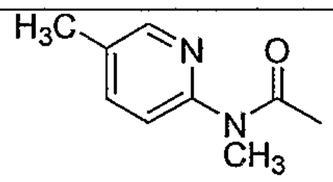
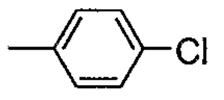
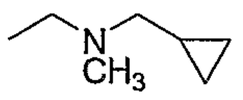
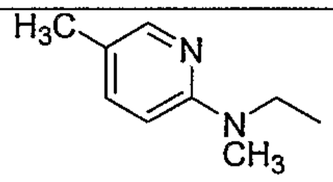
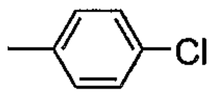
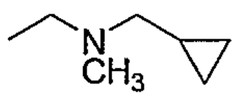
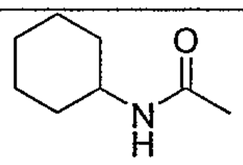
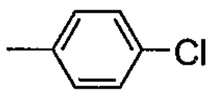
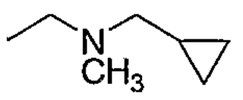
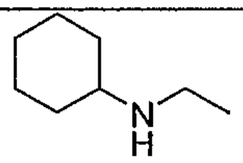
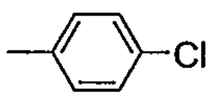
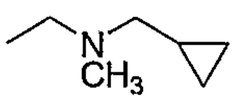
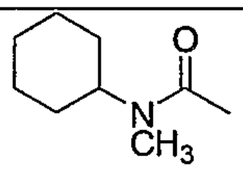
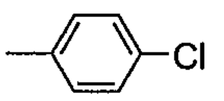
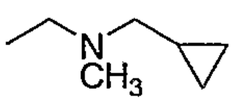
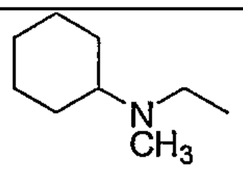
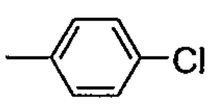
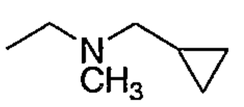
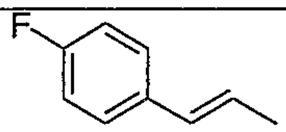
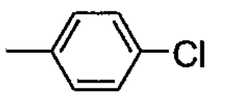
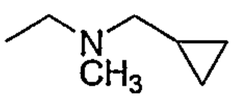
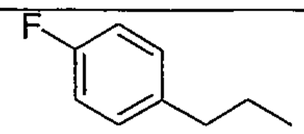
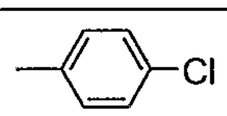
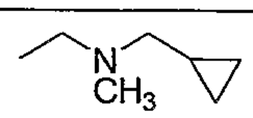
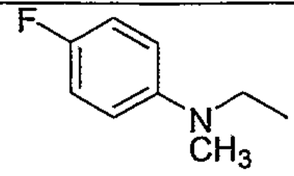
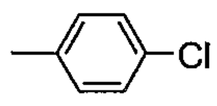
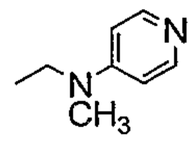
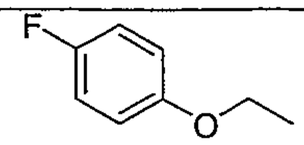
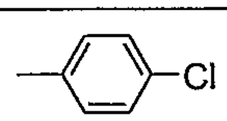
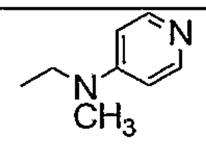
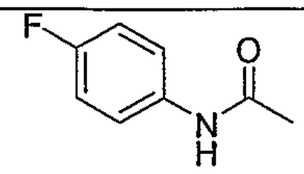
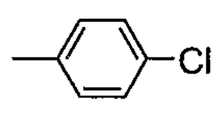
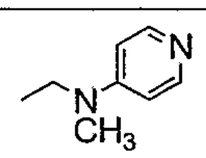
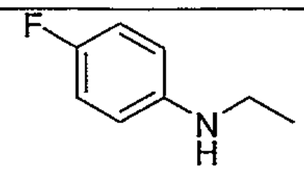
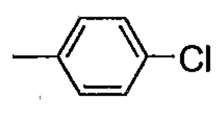
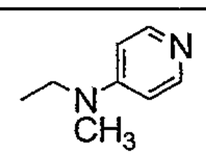
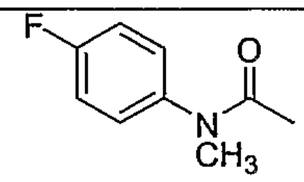
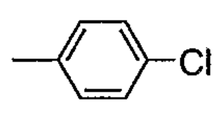
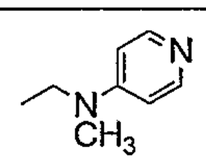
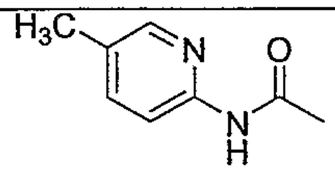
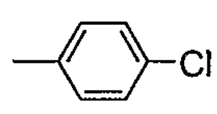
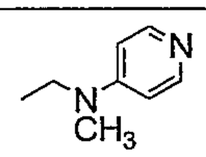
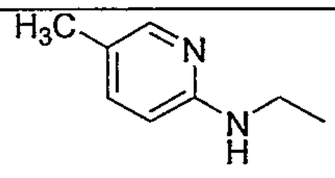
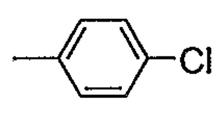
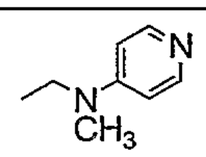
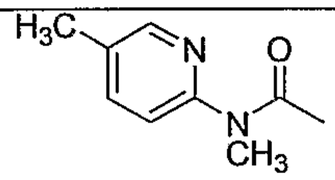
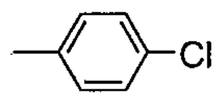
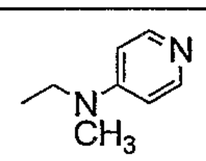
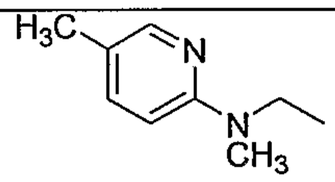
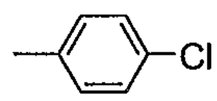
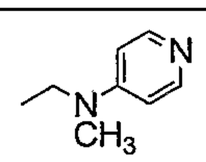
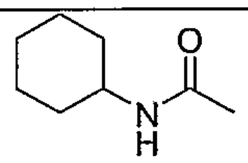
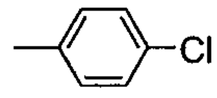
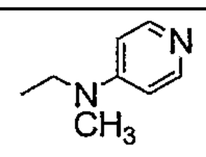
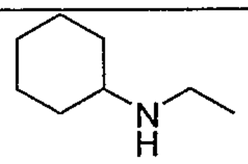
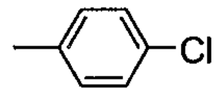
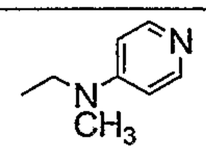
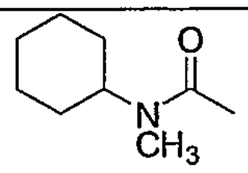
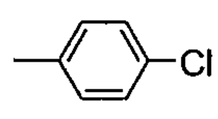
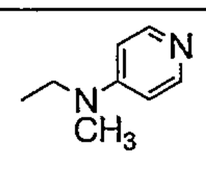
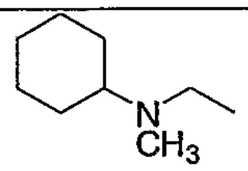
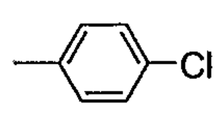
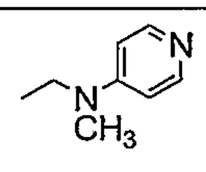
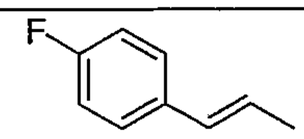
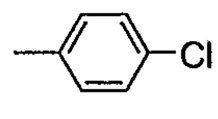
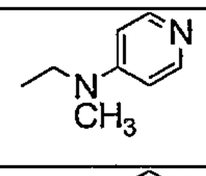
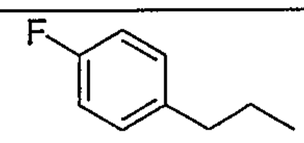
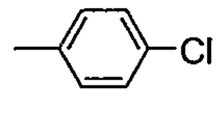
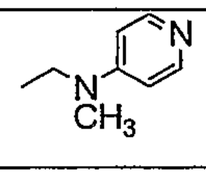
G-340		CH_3	
G-341			
G-342			
G343			

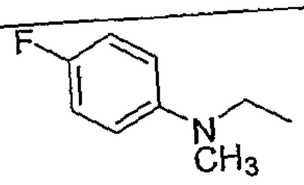
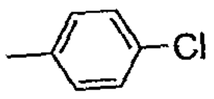
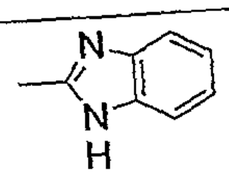
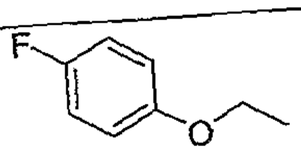
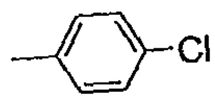
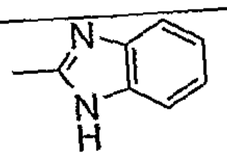
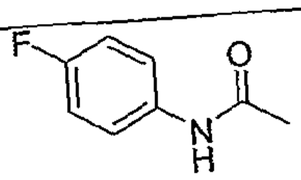
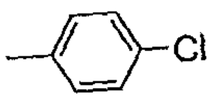
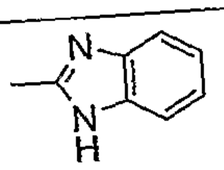
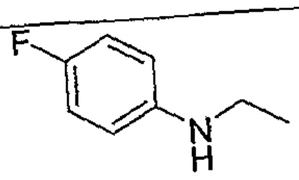
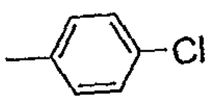
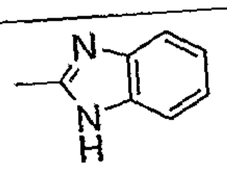
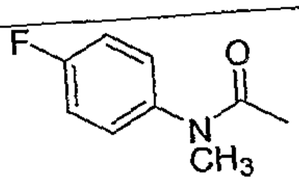
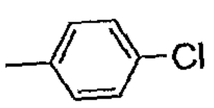
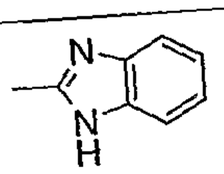
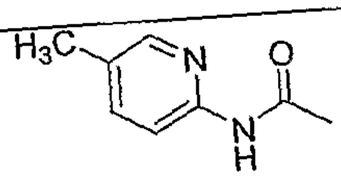
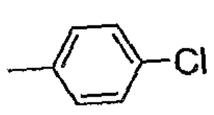
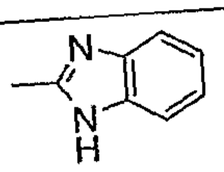
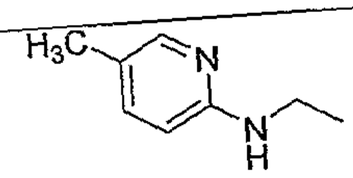
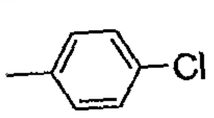
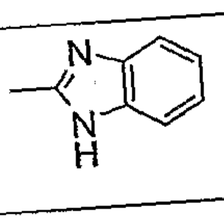
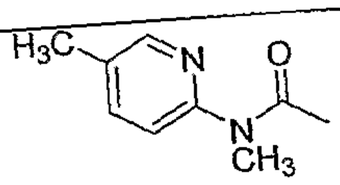
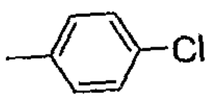
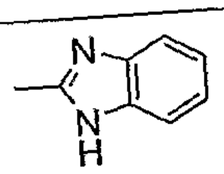
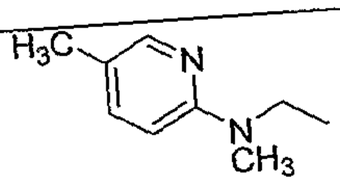
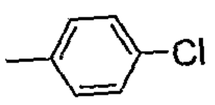
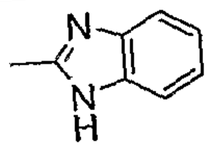
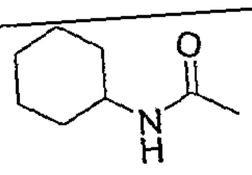
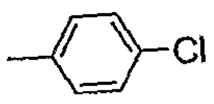
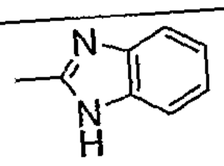
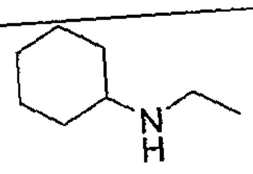
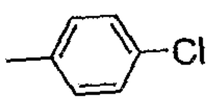
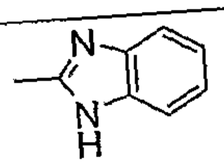
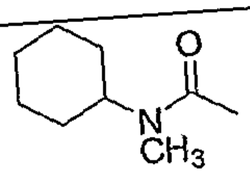
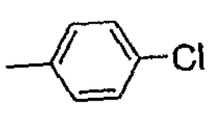
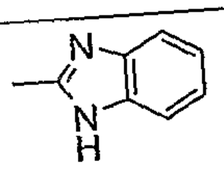
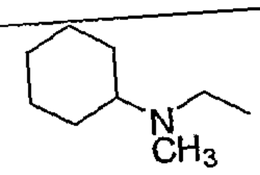
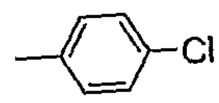
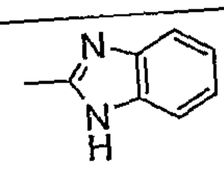
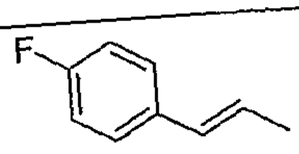
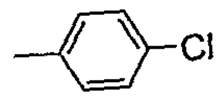
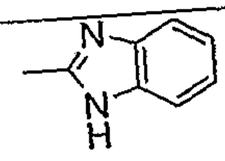
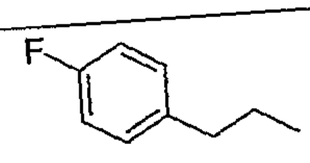
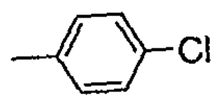
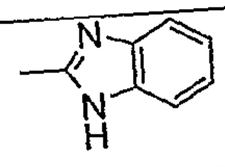
TABLE H-1A

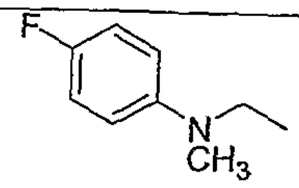
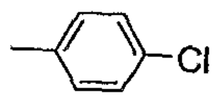
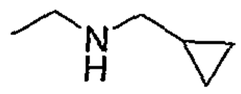
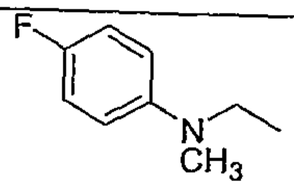
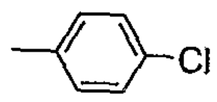
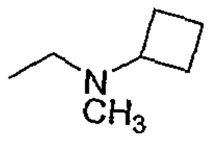
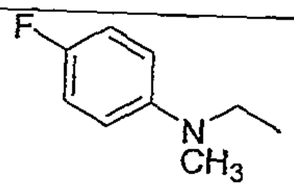
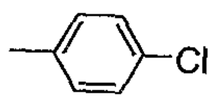
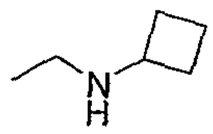
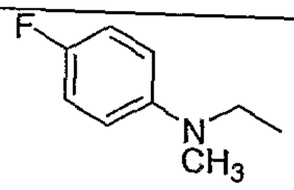
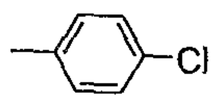
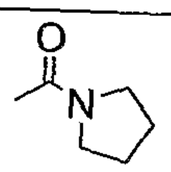
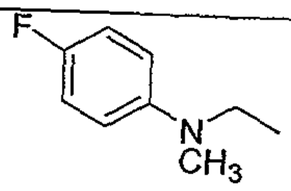
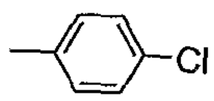
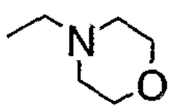
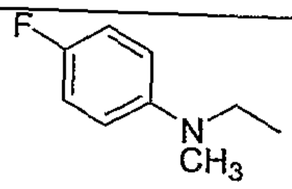
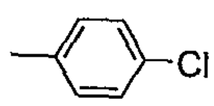
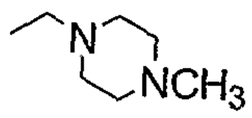
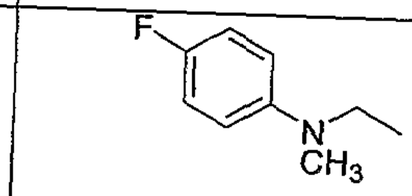
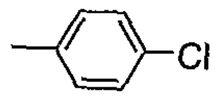
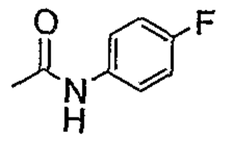
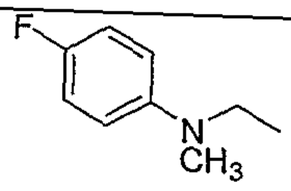
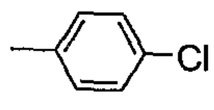
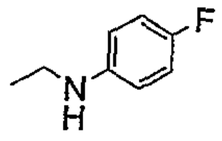
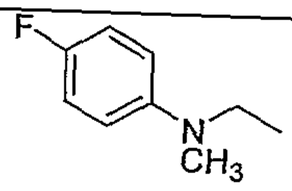
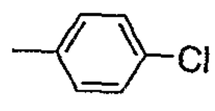
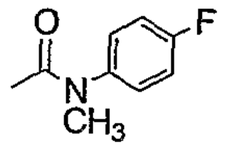
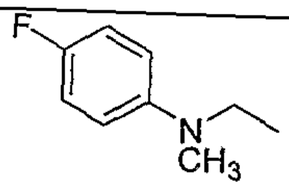
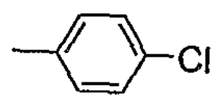
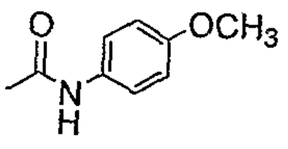
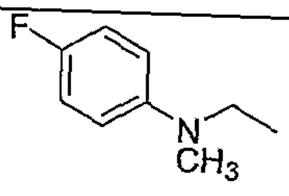
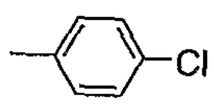
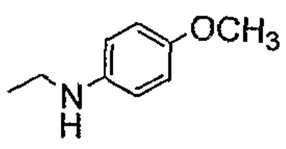
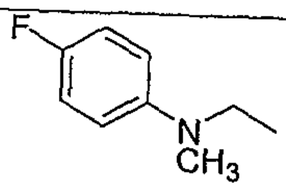
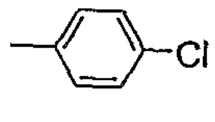
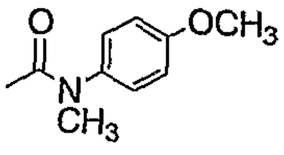
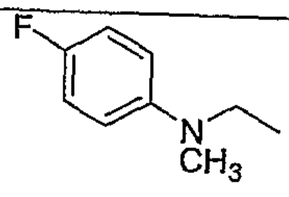
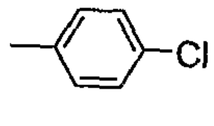
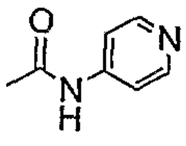
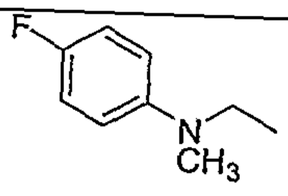
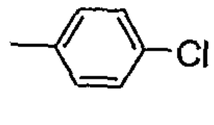
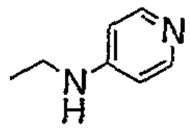


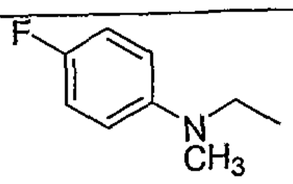
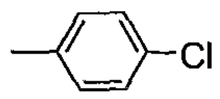
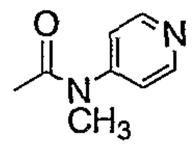
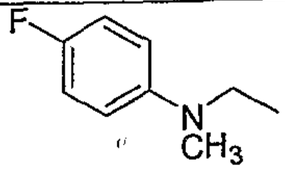
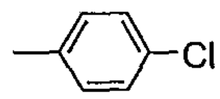
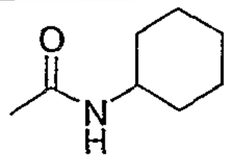
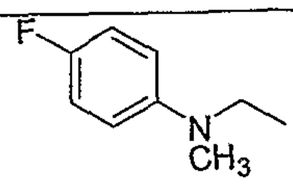
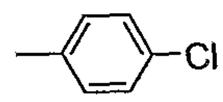
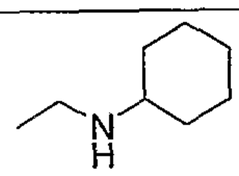
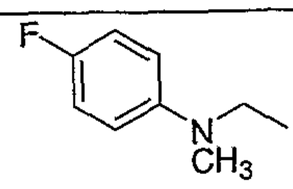
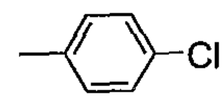
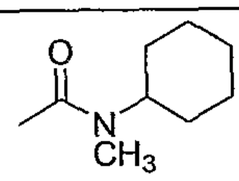
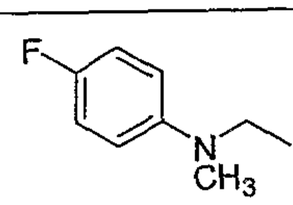
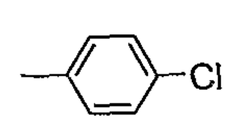
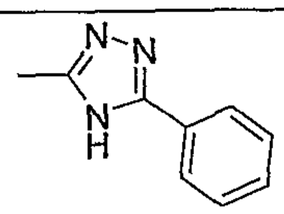
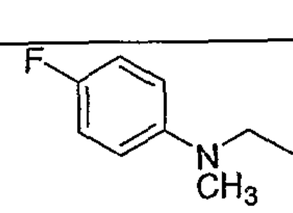
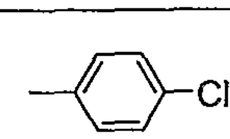
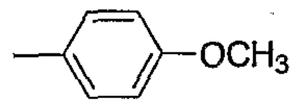
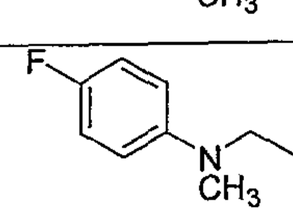
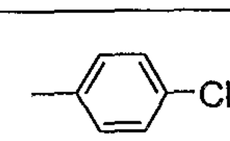
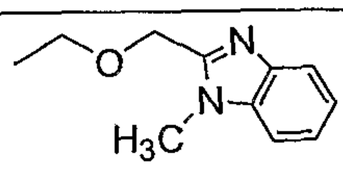
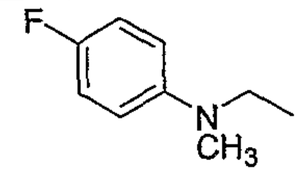
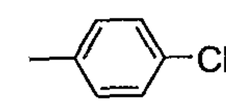
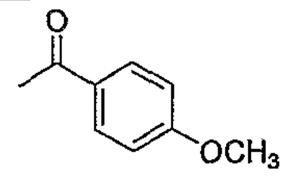
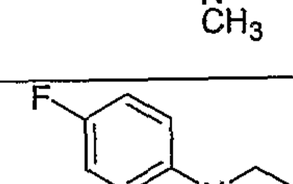
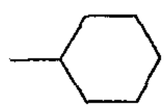
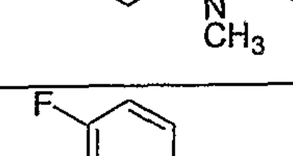
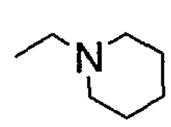
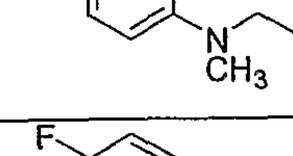
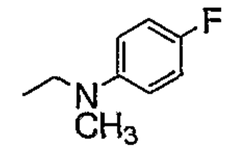
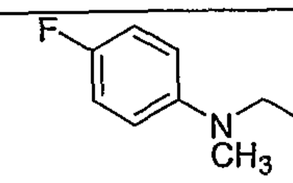
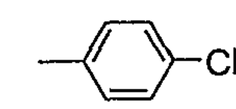
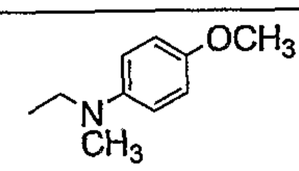
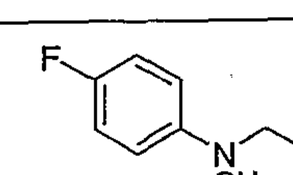
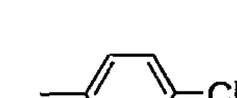
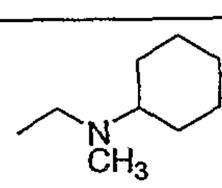
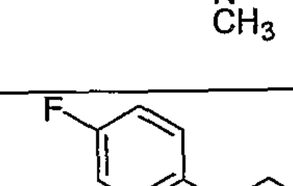
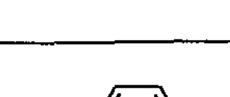
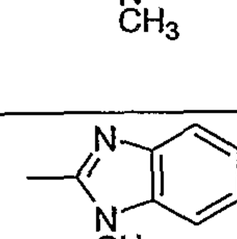
Cpd. No.	Ar^1-X-Y	R^1	R^2
H-1			
H-2			
H-3			
H-4			
H-5			
H-6			

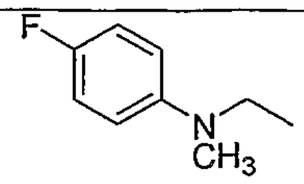
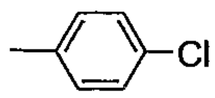
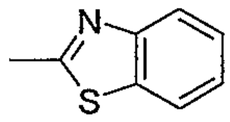
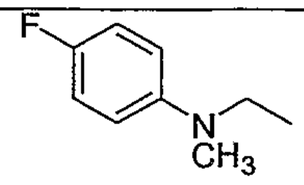
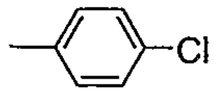
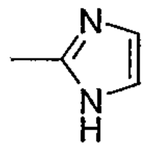
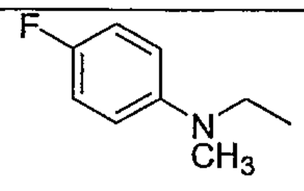
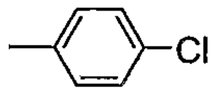
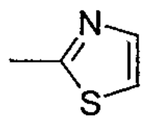
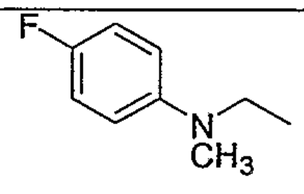
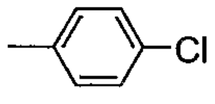
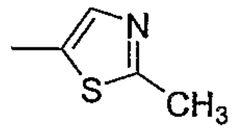
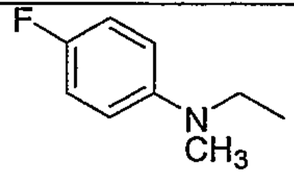
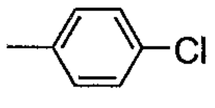
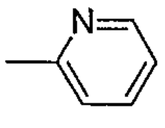
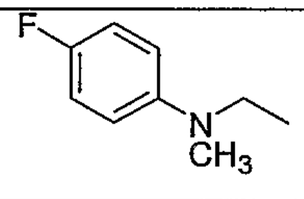
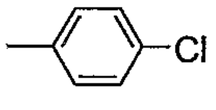
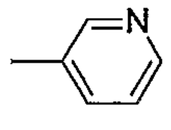
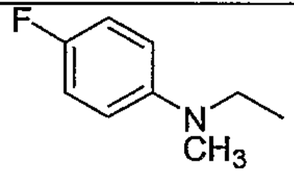
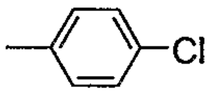
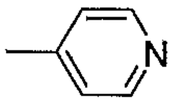
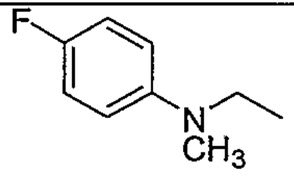
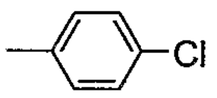
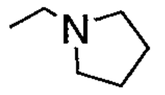
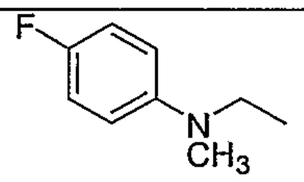
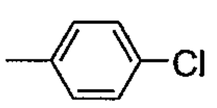
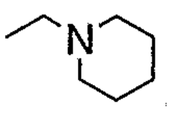
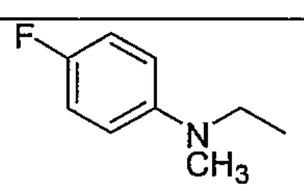
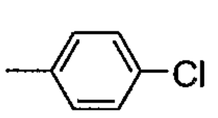
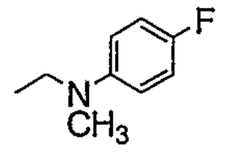
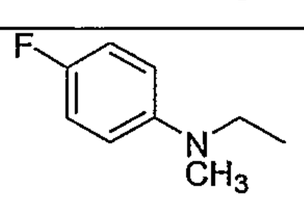
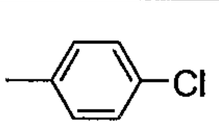
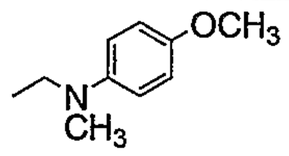
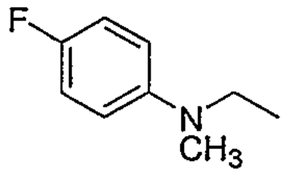
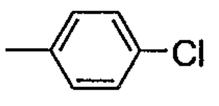
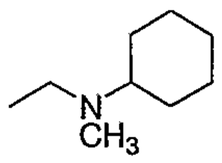
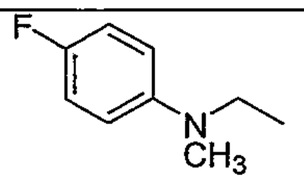
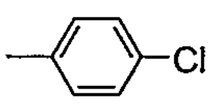
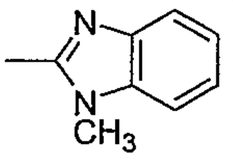
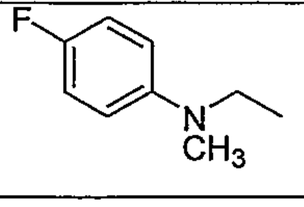
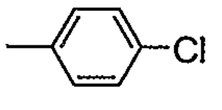
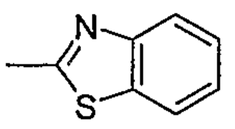
H-7			
H-8			
H-9			
H-10			
H-11			
H-12			
H-13			
H-14			
H-15			
H-16			
H-17			
H-18			
H-19			
H-20			
H-21			

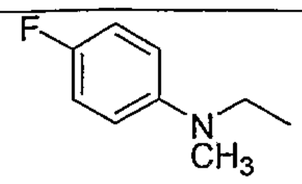
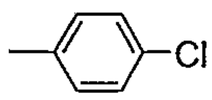
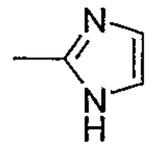
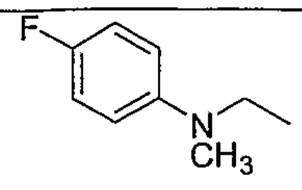
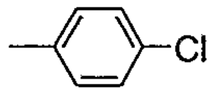
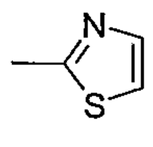
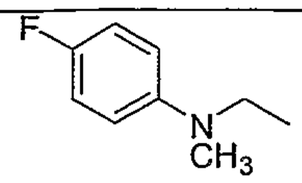
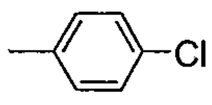
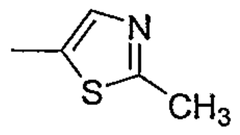
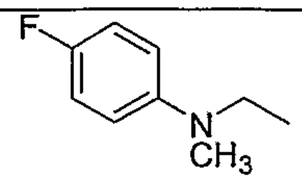
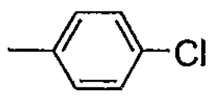
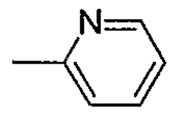
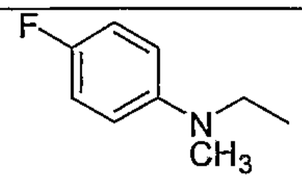
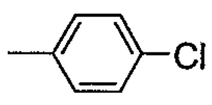
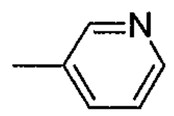
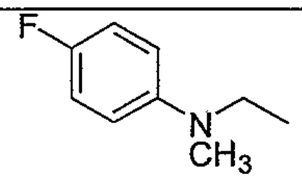
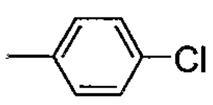
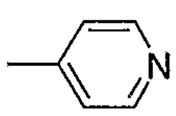
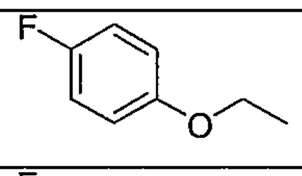
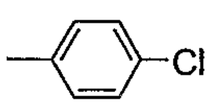
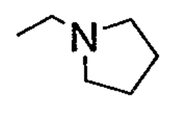
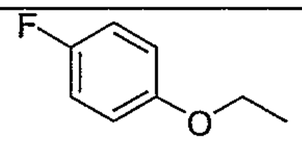
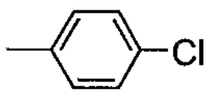
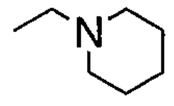
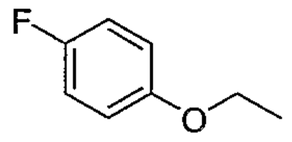
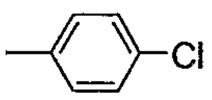
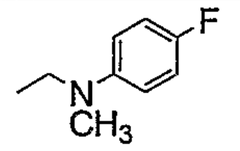
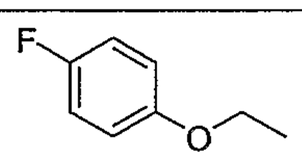
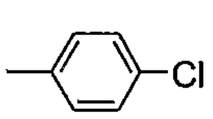
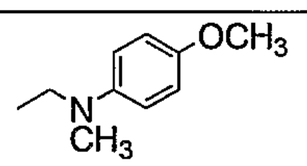
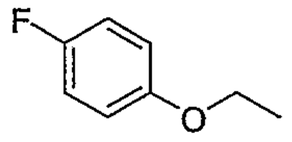
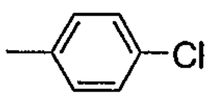
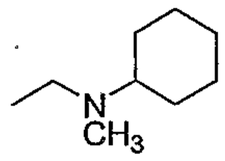
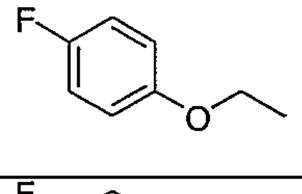
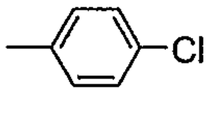
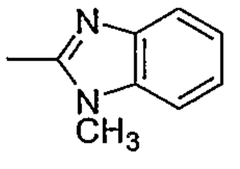
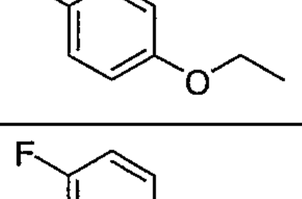
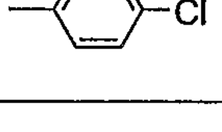
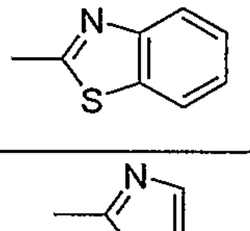
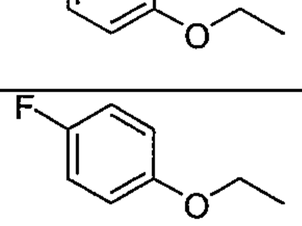
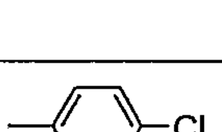
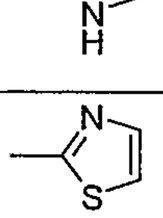
H-22			
H-23			
H-24			
H-25			
H-26			
H-27			
H-28			
H-29			
H-30			
H-31			
H-32			
H-33			
H-34			
H-35			
H-36			
H-37			

H-38			
H-39			
H-40			
H-41			
H-42			
H-43			
H-44			
H-45			
H-46			
H-47			
H-48			
H-49			
H-50			
H-51			
H-52			

H-53			
H-54			
H-55			
H-56			
H-57			
H-58			
H-59			
H-60			
H-61			
H-62			
H-63			
H-64			
H-65			
H-66			

H-67			
H-68			
H-69			
H-70			
H-71			
H-72			
H-73			
H-74			
H-75			
H-76			
H-77			
H-78			
H-79			
H-80			

H-81			
H-82			
H-83			
H-84			
H-85			
H-86			
H-87			
H-88			
H-89			
H-90			
H-91			
H-92			
H-93			
H-94			

H-95			
H-96			
H-97			
H-98			
H-99			
H-100			
H-101			
H-102			
H-103			
H-104			
H-105			
H-106			
H-107			
H-108			
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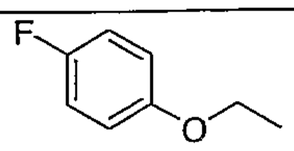
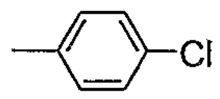
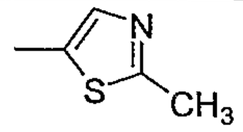
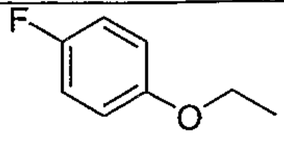
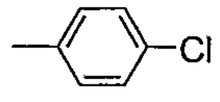
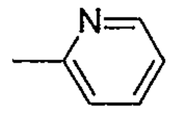
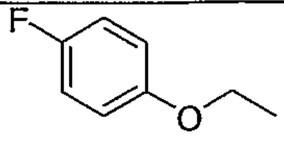
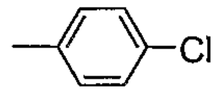
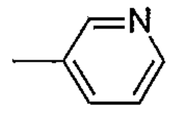
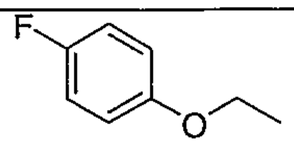
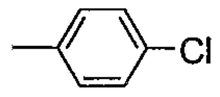
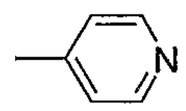
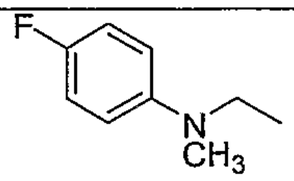
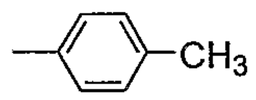
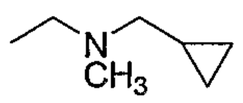
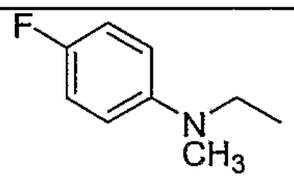
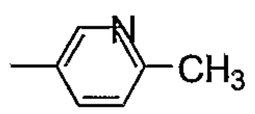
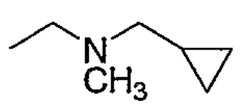
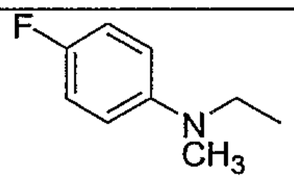
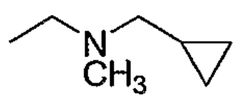
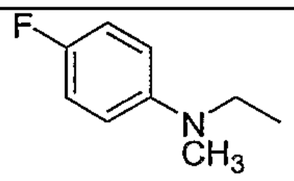
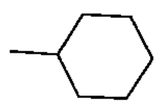
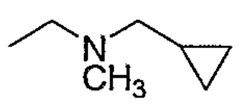
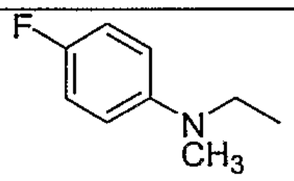
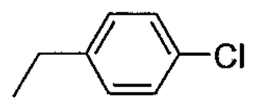
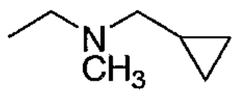
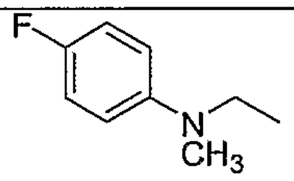
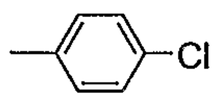
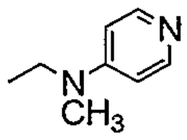
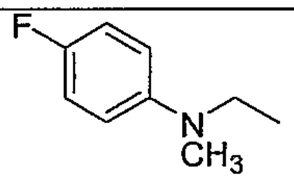
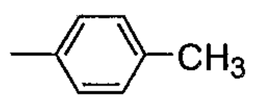
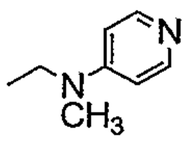
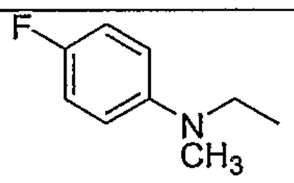
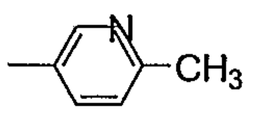
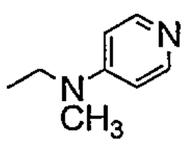
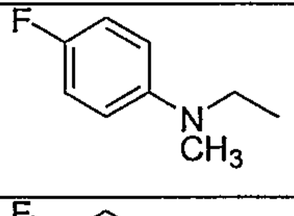
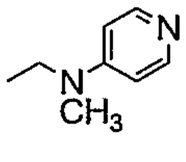
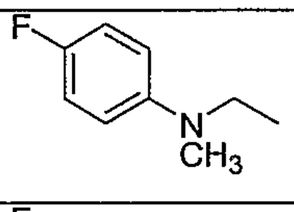
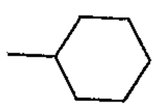
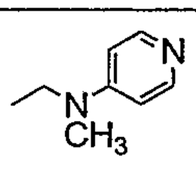
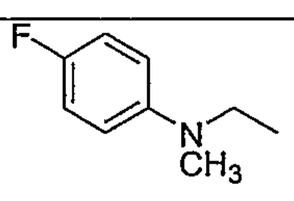
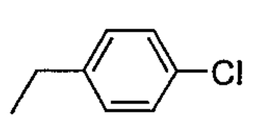
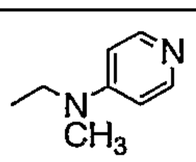
H-110			
H-111			
H-112			
H-113			
H-114			
H-115			
H-116		CH_3	
H-117			
H-118			
H-119			
H-120			
H-121			
H-122		CH_3	
H-123			
H-124			

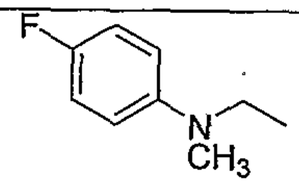
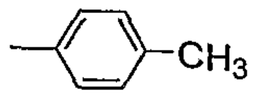
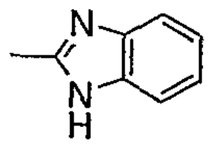
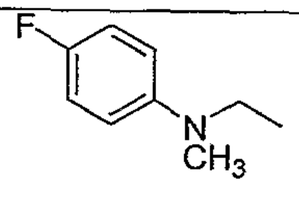
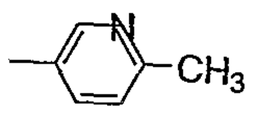
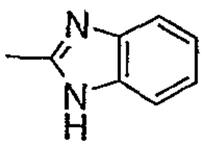
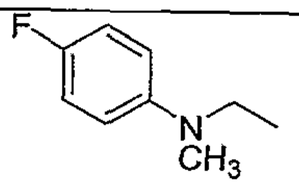
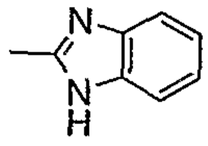
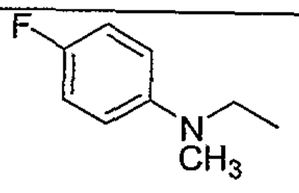
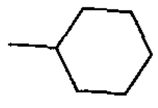
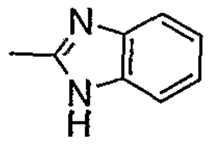
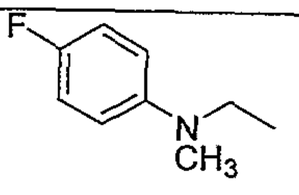
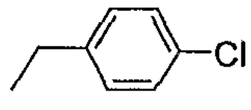
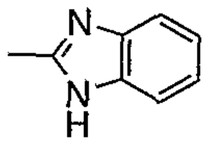
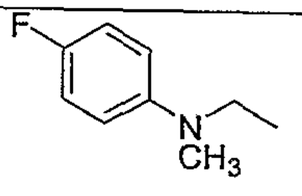
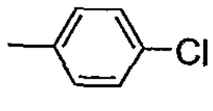
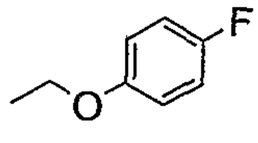
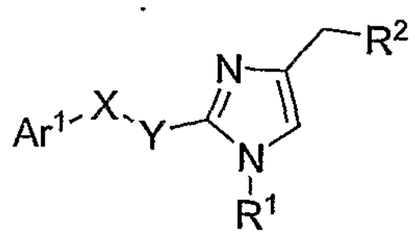
H-125			
H-126			
H-127		CH_3	
H-128			
H-129			
H130			

TABLE H-1B



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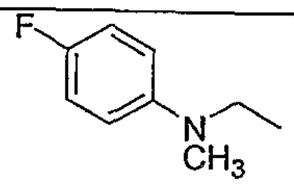
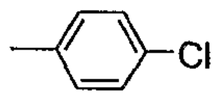
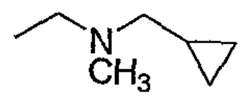
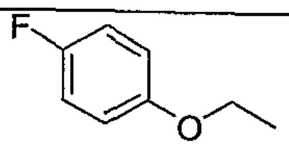
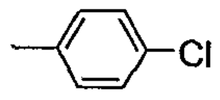
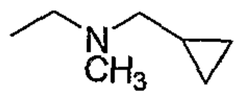
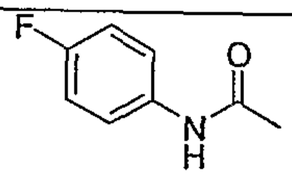
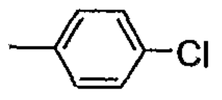
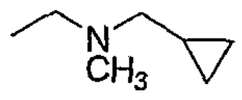
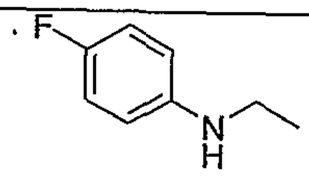
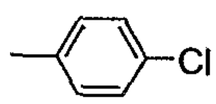
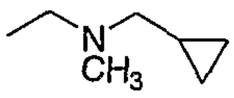
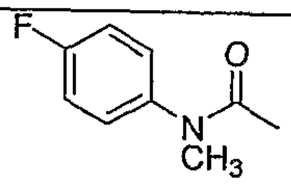
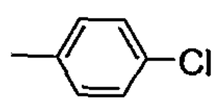
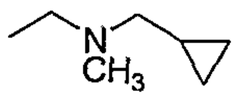
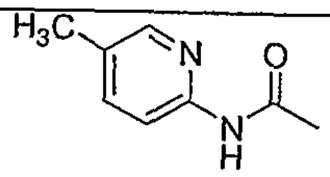
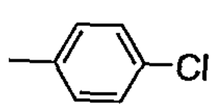
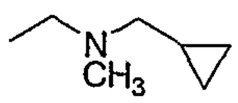
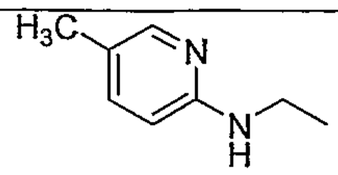
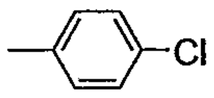
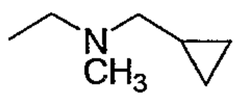
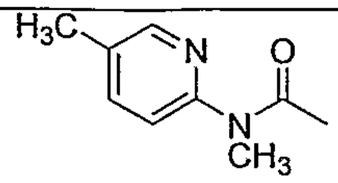
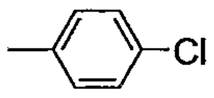
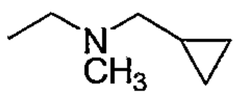
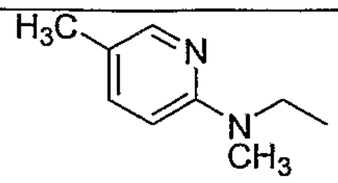
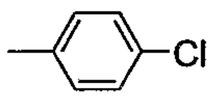
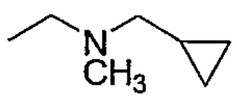
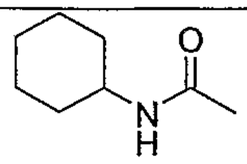
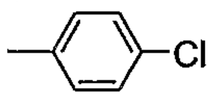
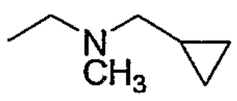
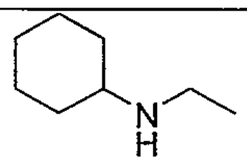
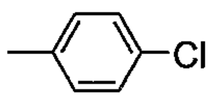
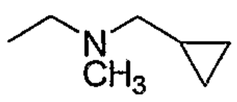
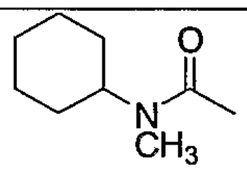
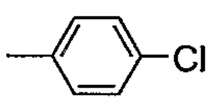
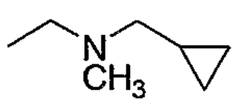
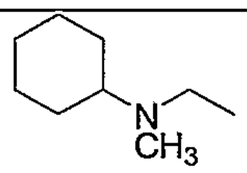
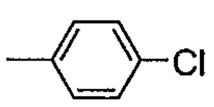
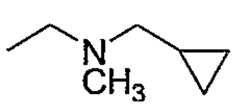
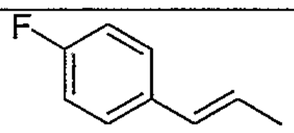
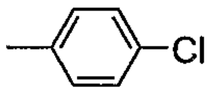
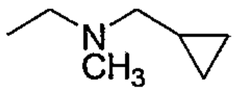
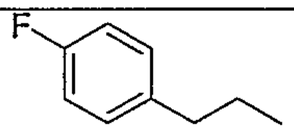
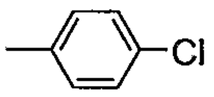
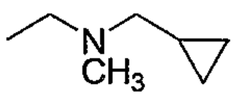
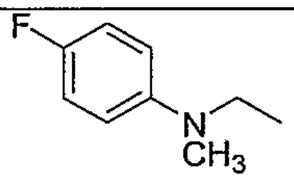
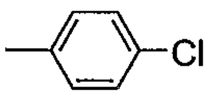
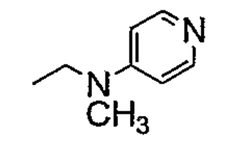
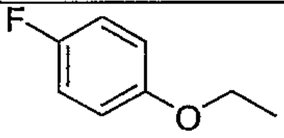
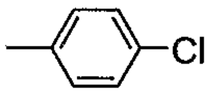
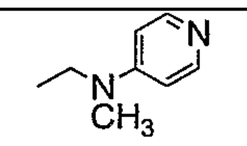
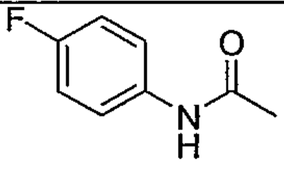
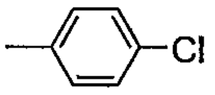
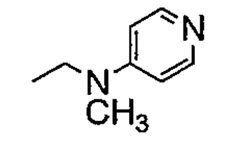
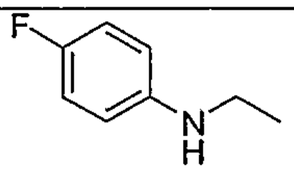
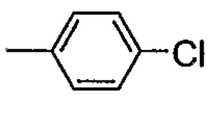
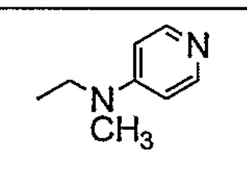
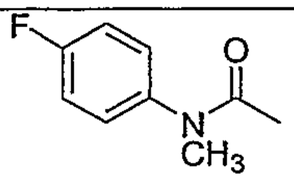
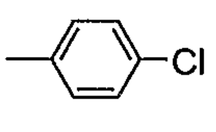
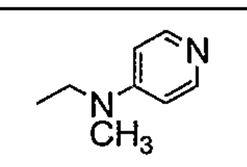
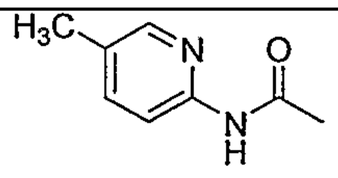
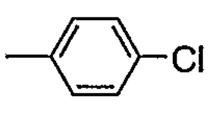
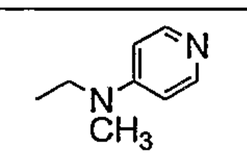
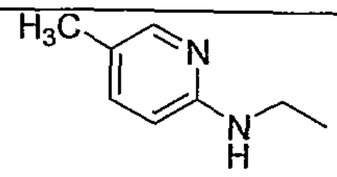
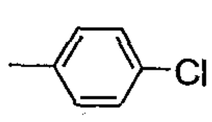
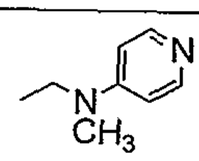
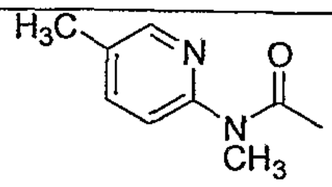
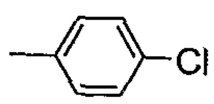
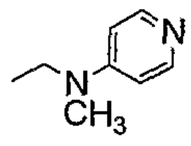
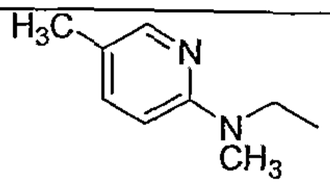
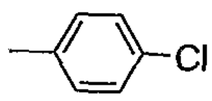
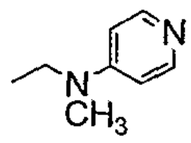
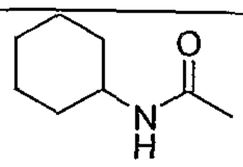
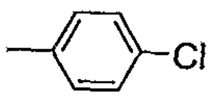
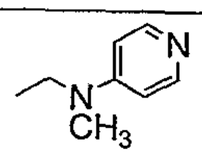
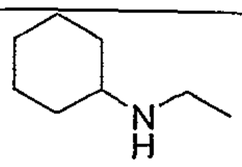
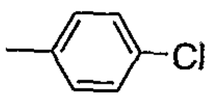
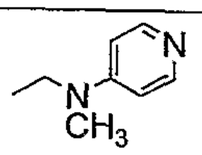
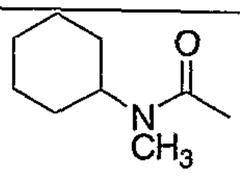
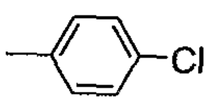
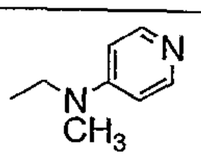
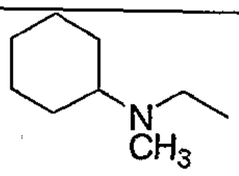
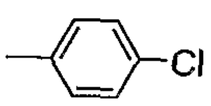
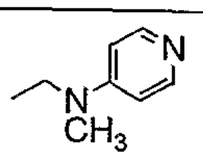
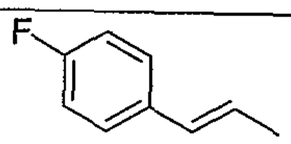
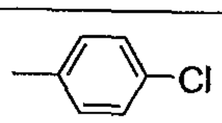
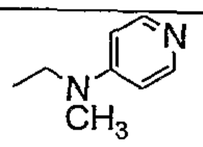
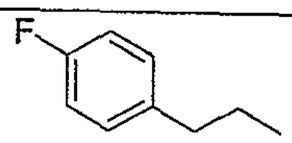
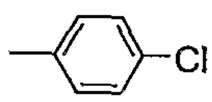
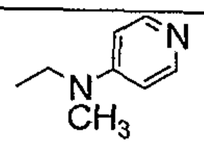
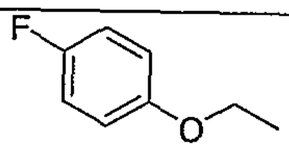
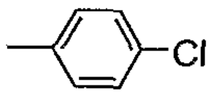
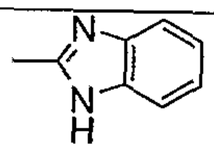
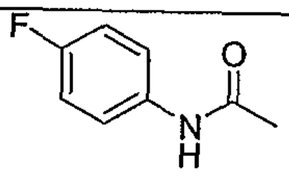
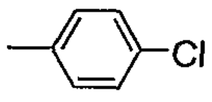
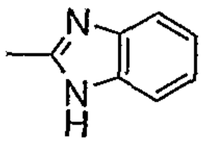
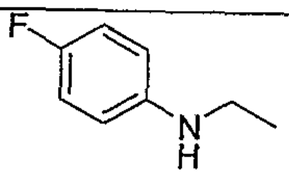
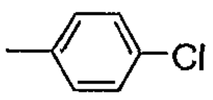
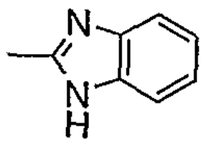
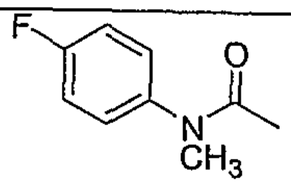
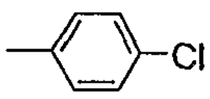
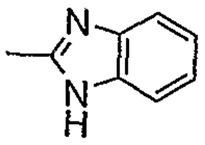
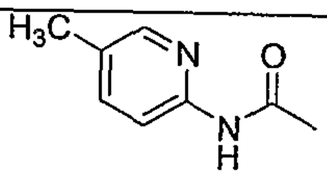
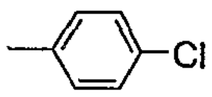
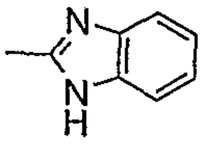
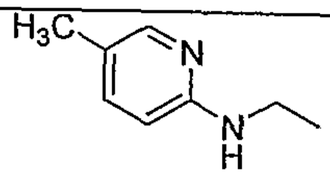
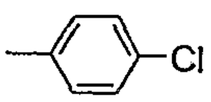
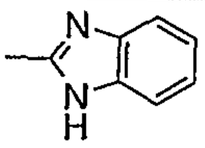
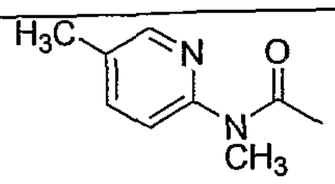
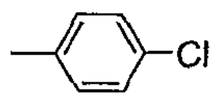
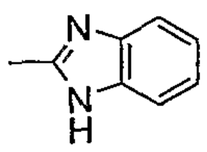
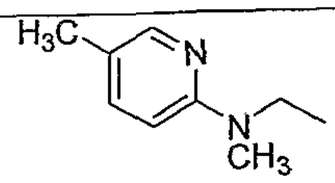
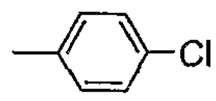
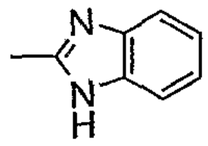
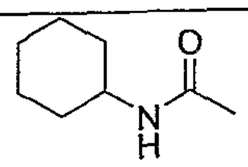
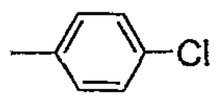
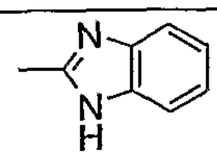
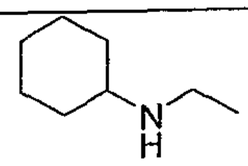
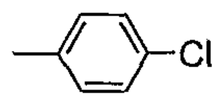
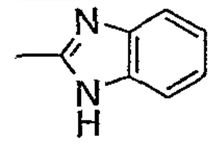
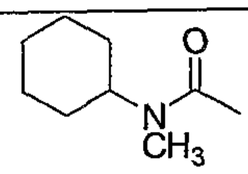
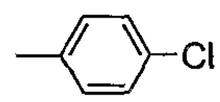
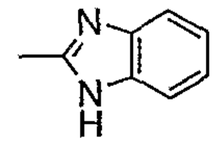
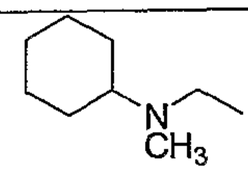
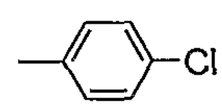
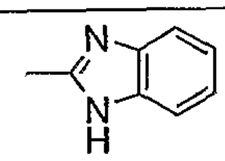
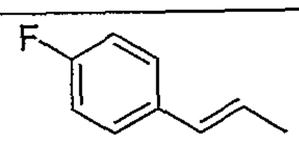
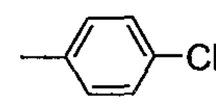
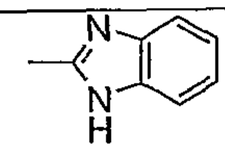
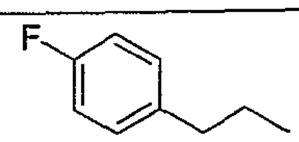
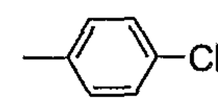
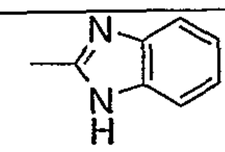
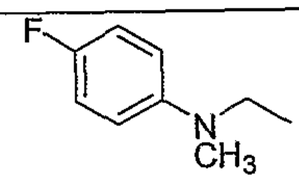
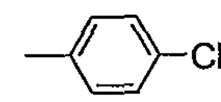
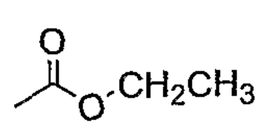
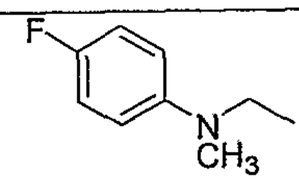
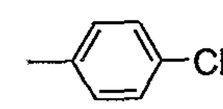
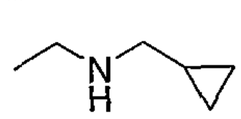
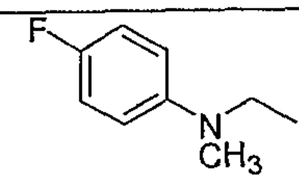
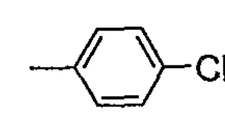
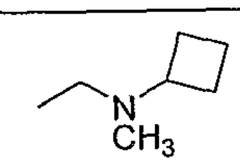
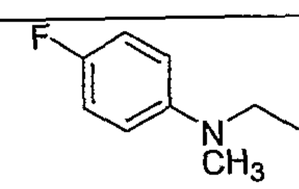
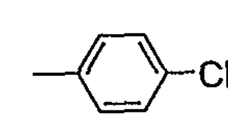
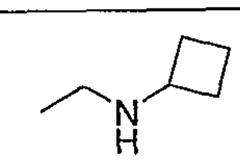
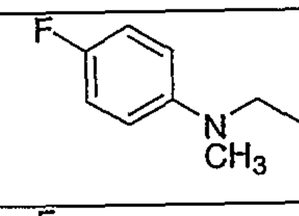
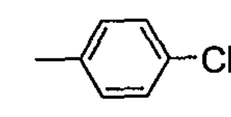
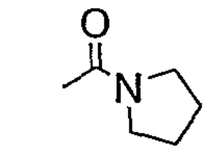
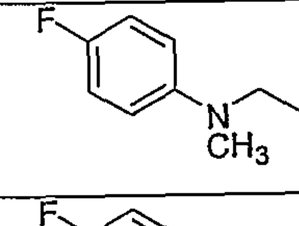
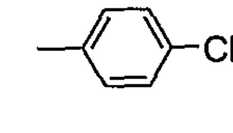
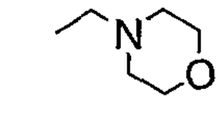
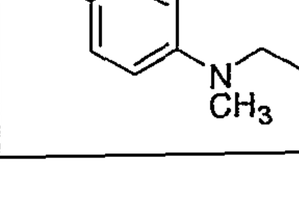
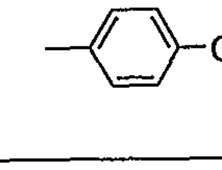
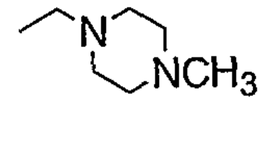
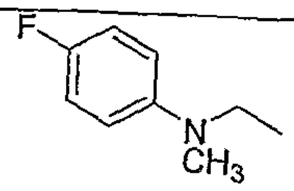
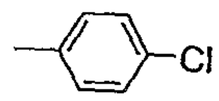
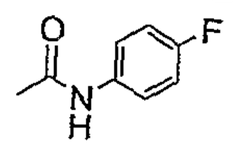
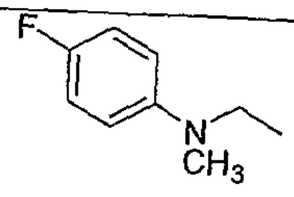
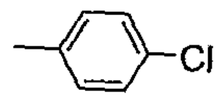
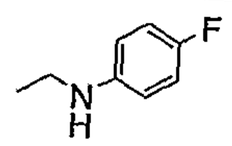
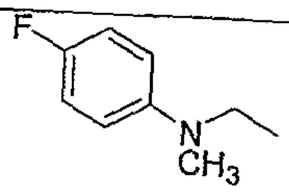
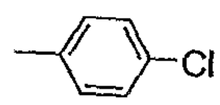
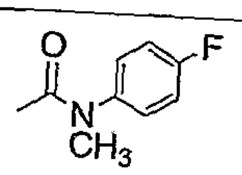
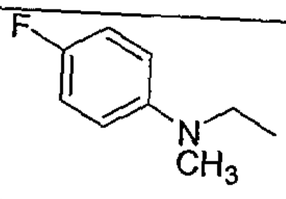
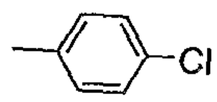
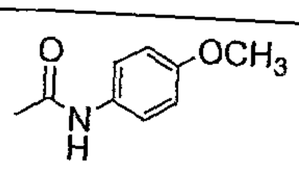
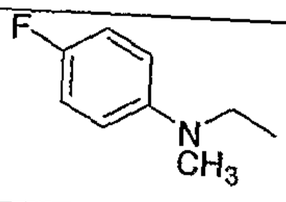
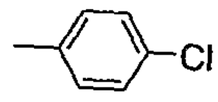
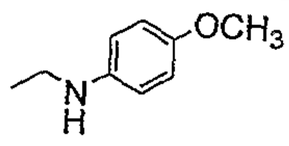
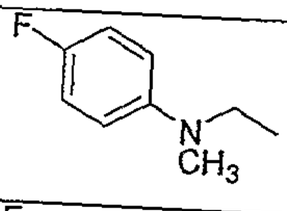
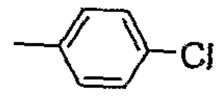
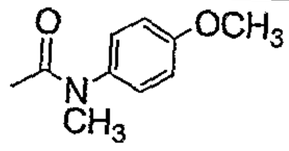
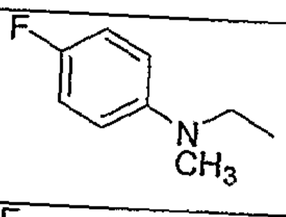
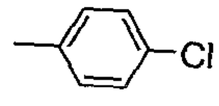
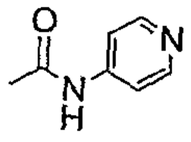
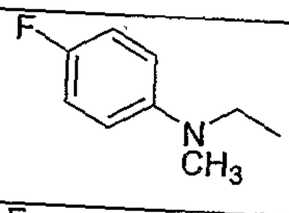
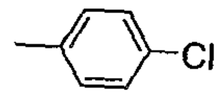
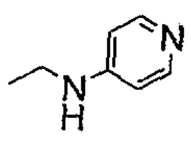
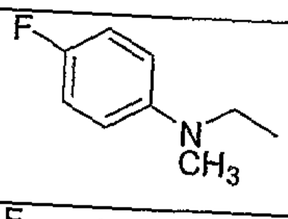
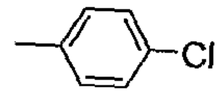
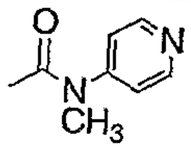
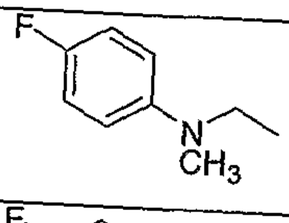
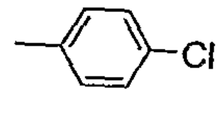
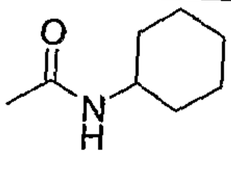
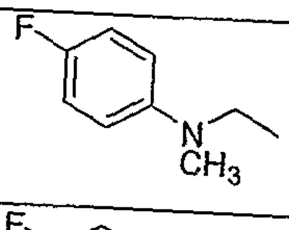
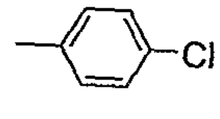
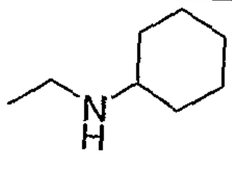
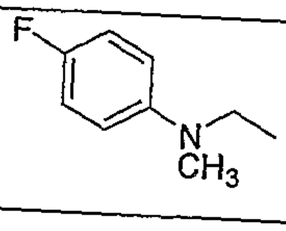
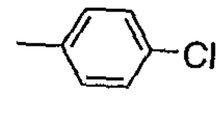
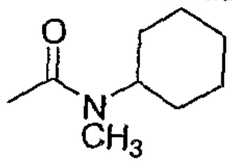
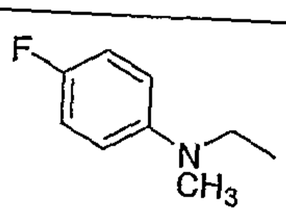
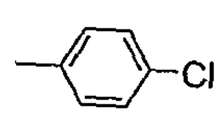
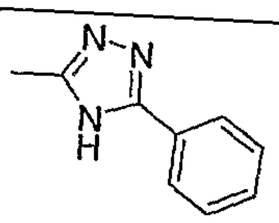
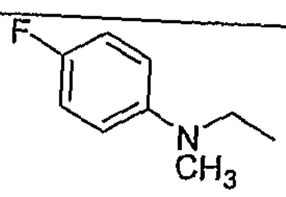
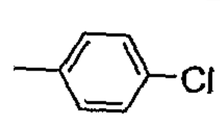
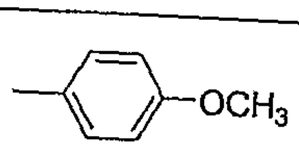
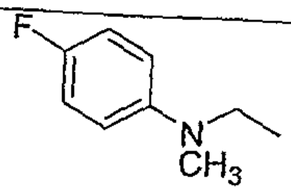
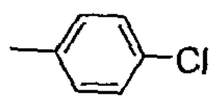
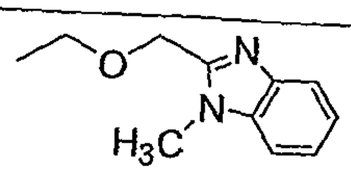
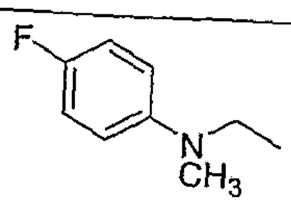
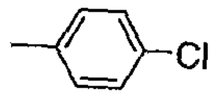
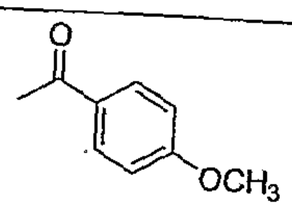
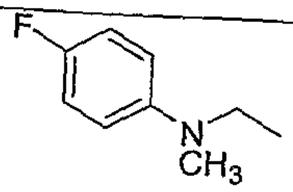
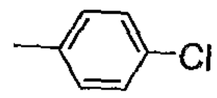
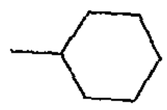
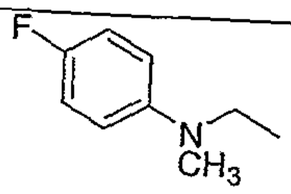
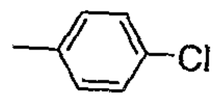
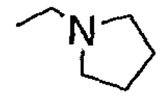
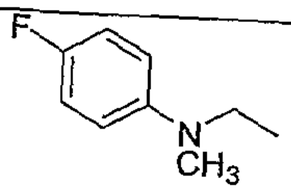
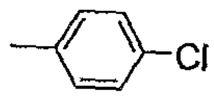
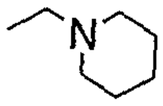
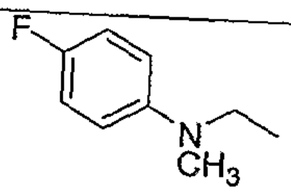
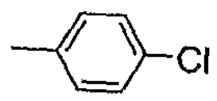
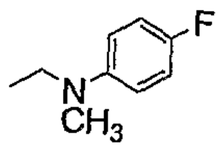
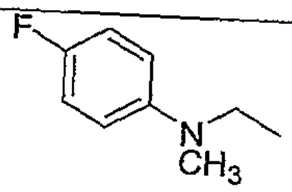
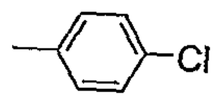
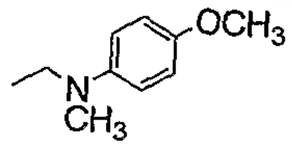
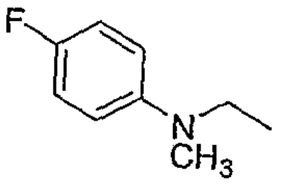
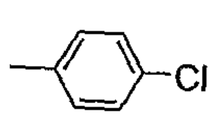
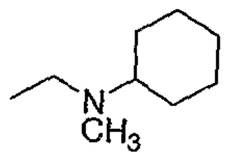
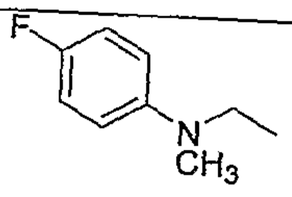
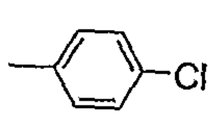
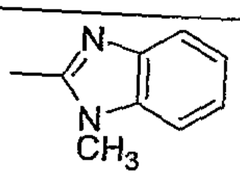
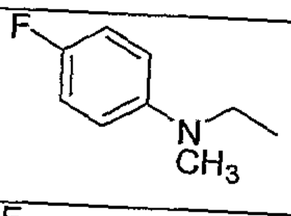
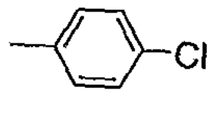
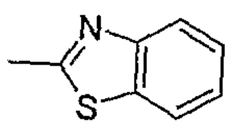
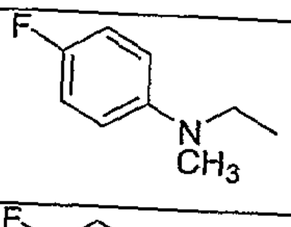
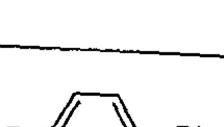
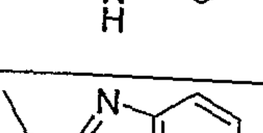
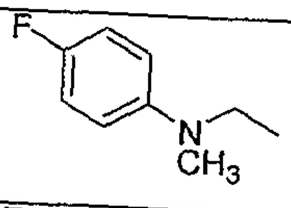
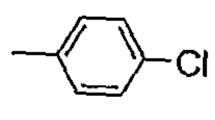
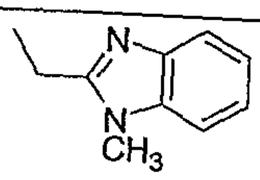
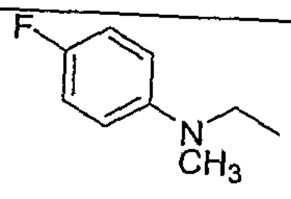
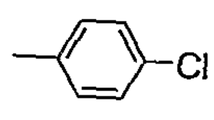
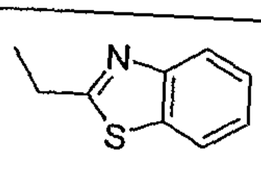
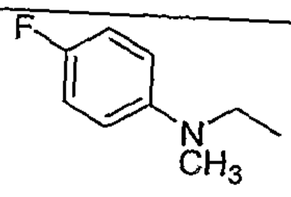
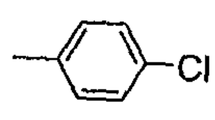
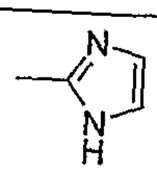
H-131			
H-132			
H-133			
H-134			
H-135			
H-136			

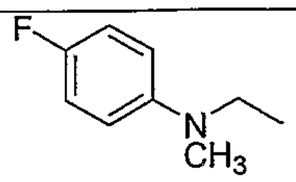
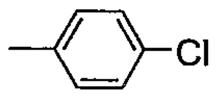
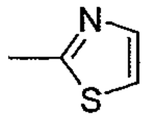
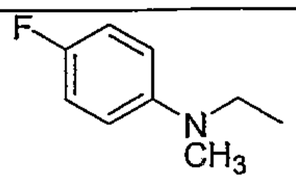
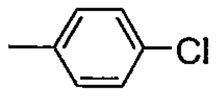
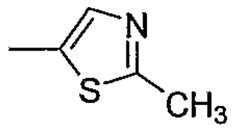
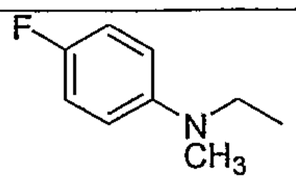
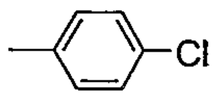
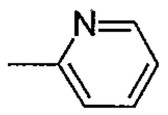
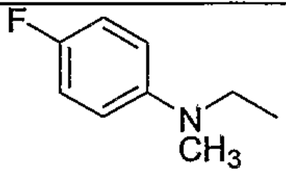
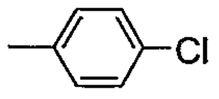
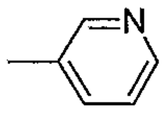
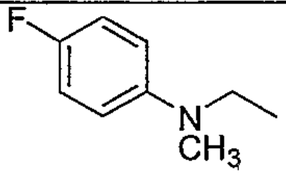
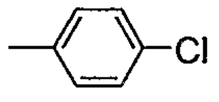
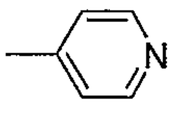
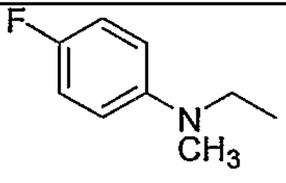
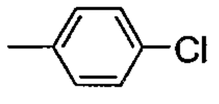
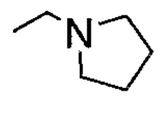
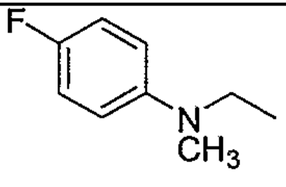
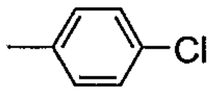
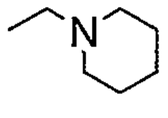
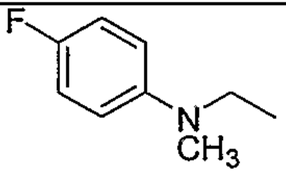
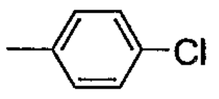
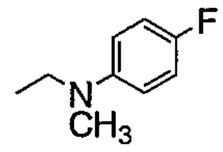
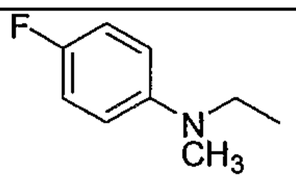
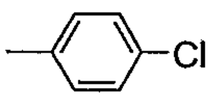
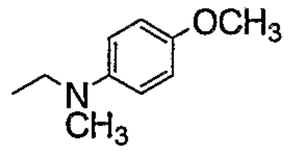
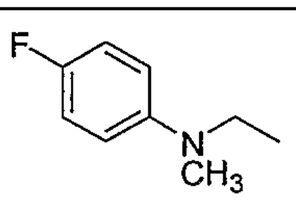
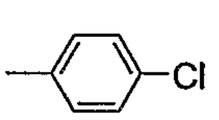
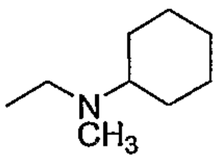
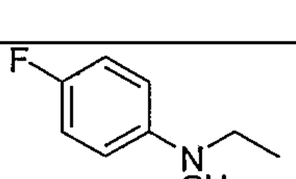
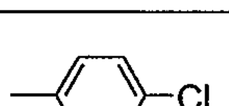
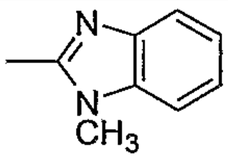
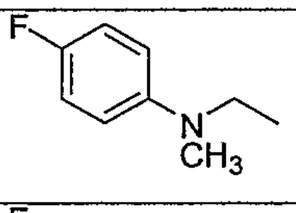
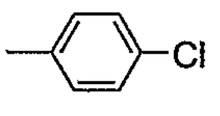
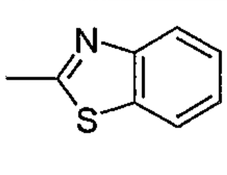
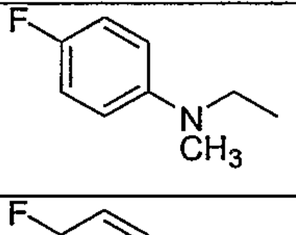
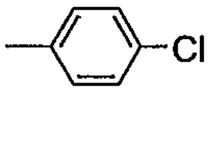
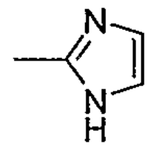
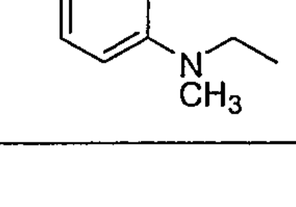
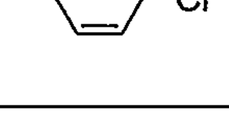
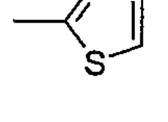
H-137			
H-138			
H-139			
H-140			
H-141			
H-142			
H-143			
H-144			
H-145			
H-146			
H-147			
H-148			
H-149			
H-150			
H-151			

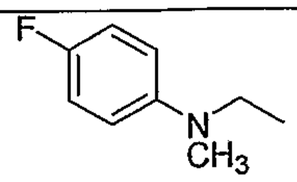
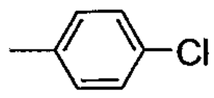
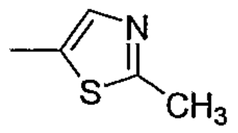
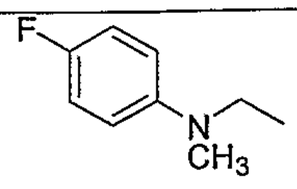
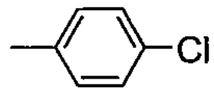
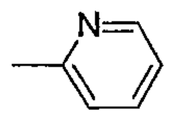
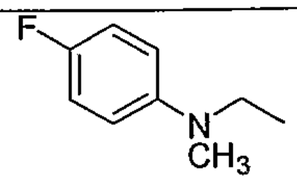
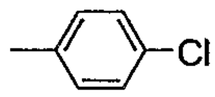
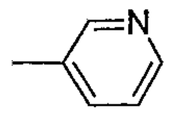
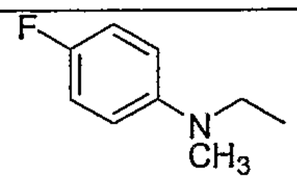
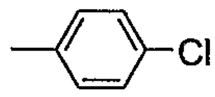
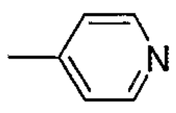
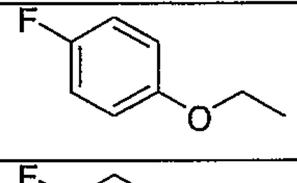
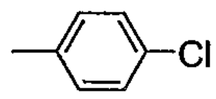
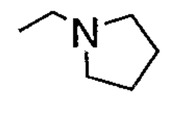
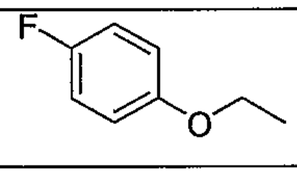
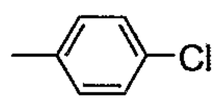
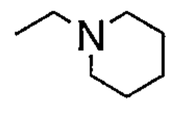
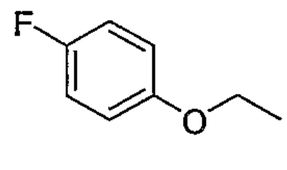
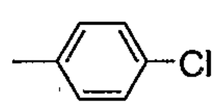
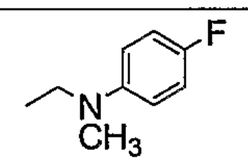
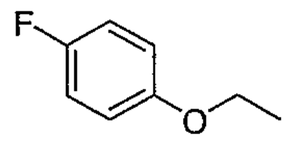
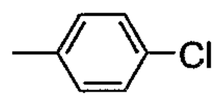
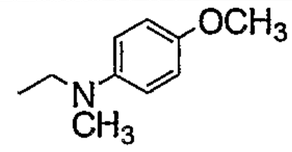
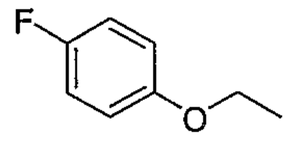
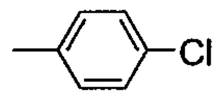
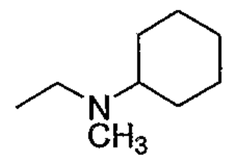
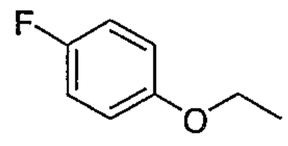
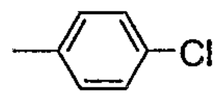
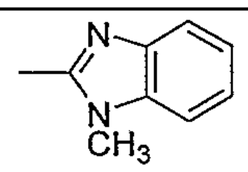
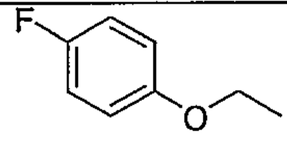
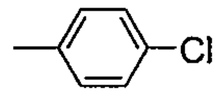
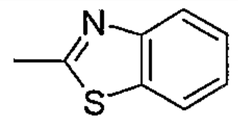
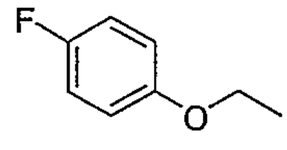
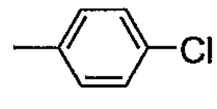
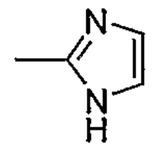
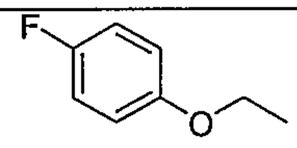
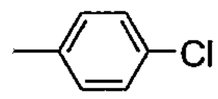
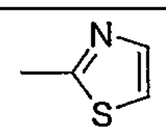
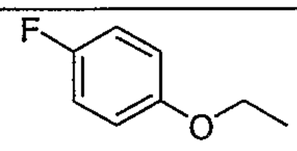
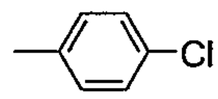
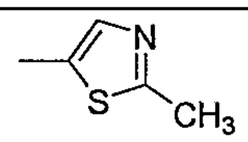
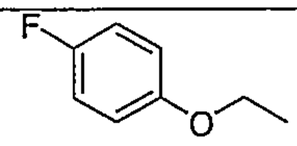
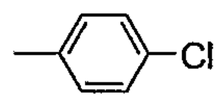
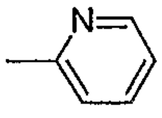
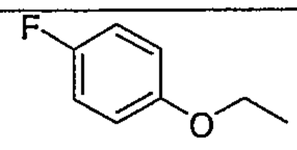
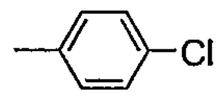
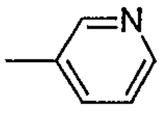
H-152			
H-153			
H-154			
H-155			
H-156			
H-157			
H-158			
H-159			
H-160			
H-161			
H-162			
H-163			
H-164			
H-165			
H-166			

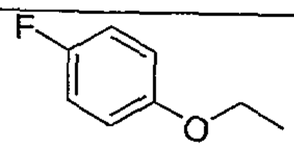
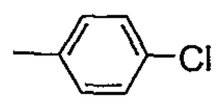
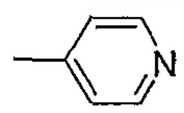
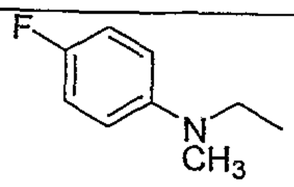
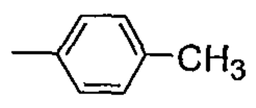
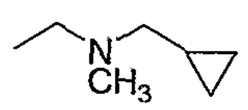
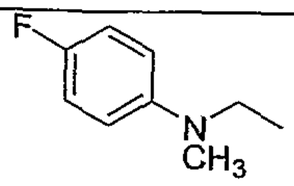
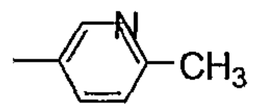
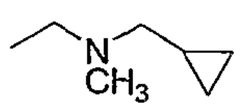
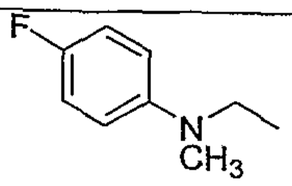
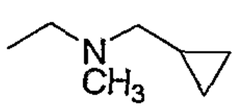
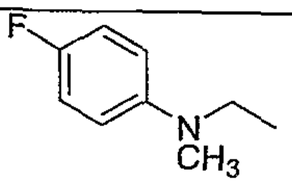
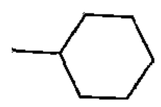
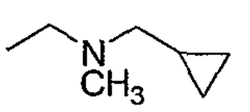
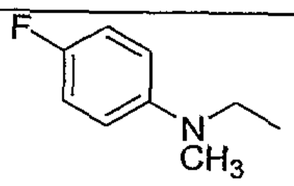
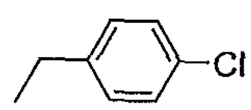
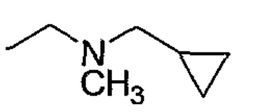
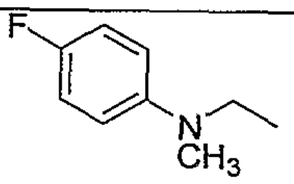
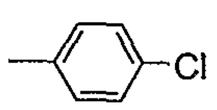
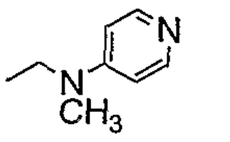
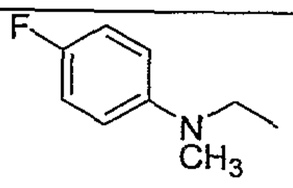
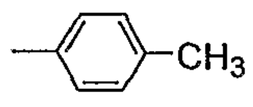
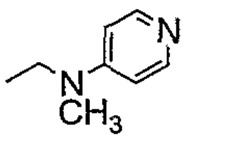
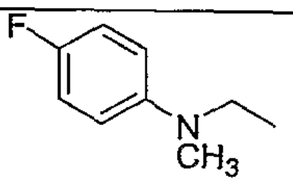
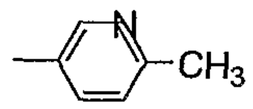
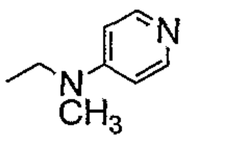
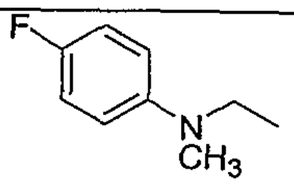
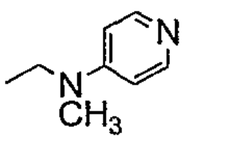
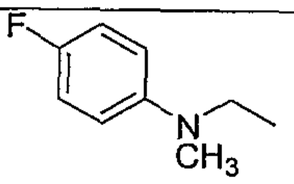
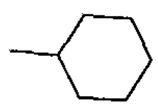
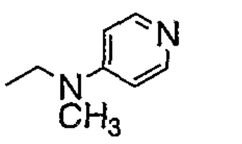
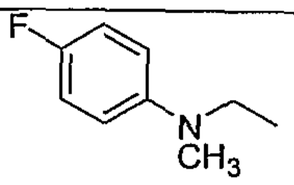
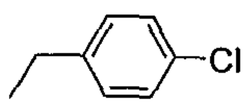
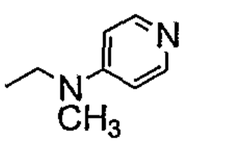
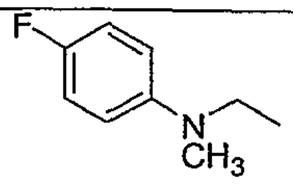
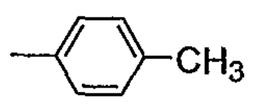
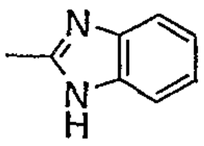
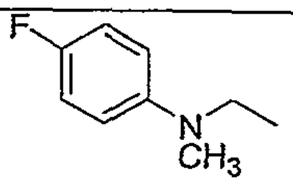
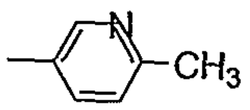
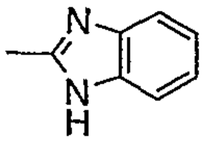
H-167			
H-168			
H-169			
H-170			
H-171			
H-172			
H-173			
H-174			
H-175			
H-176			
H-177			
H-178			
H-179			
H-180			
H-181			

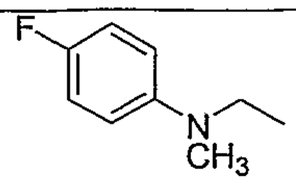
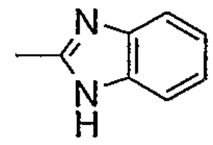
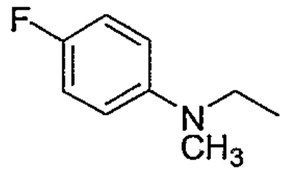
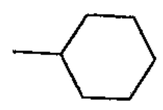
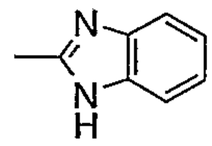
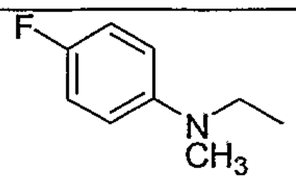
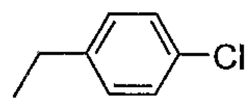
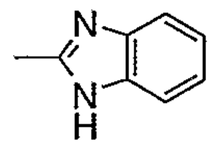
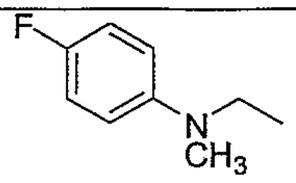
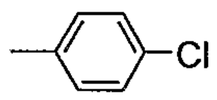
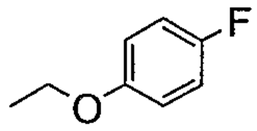
H-182			
H-183			
H-184			
H-185			
H-186			
H-187			
H-188			
H-189			
H-190			
H-191			
H-192			
H-193			
H-194			
H-195			

H-196			
H-197			
H-198			
H-199			
H-200			
H-201			
H-202			
H-203			
H-204			
H-205			
H-206			
H-207			
H-208			
H-209			

H-210			
H-211			
H-212			
H-213			
H-214			
H-215			
H-216			
H-217			
H-218			
H-219			
H-220			
H-221			
H-222			
H-223			

H-224			
H-225			
H-226			
H-227			
H-228			
H-229			
H-230			
H-231			
H-232			
H-233			
H-234			
H-235			
H-236			
H-237			
H-238			
H-239			

H-240			
H-241			
H-242			
H-243		CH_3	
H-244			
H-245			
H-246			
H-247			
H-248			
H-249		CH_3	
H-250			
H-251			
H-252			
H-253			

H-254		CH_3	
H-255			
H-256			
H257			

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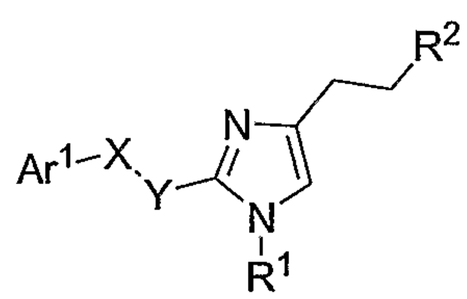

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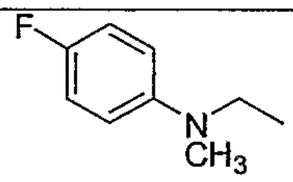
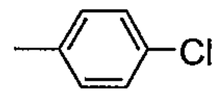
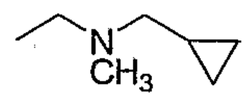
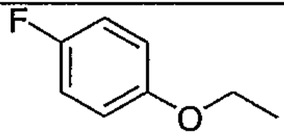
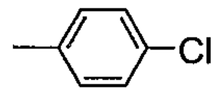
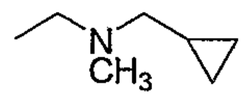
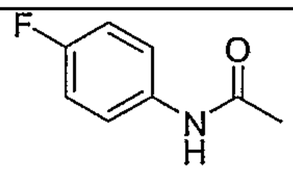
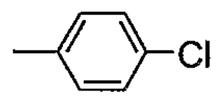
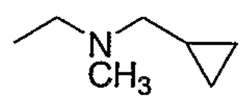
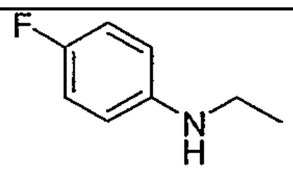
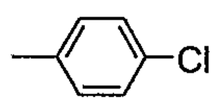
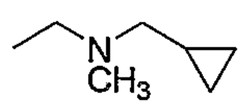
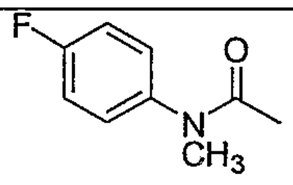
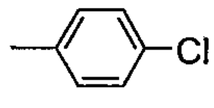
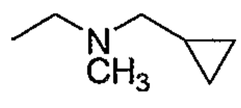
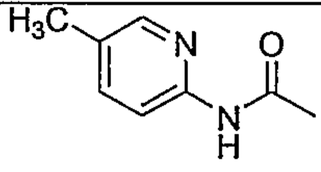
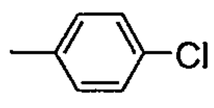
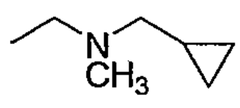
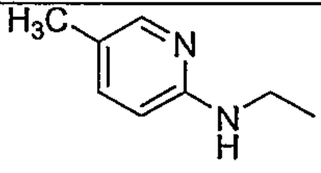
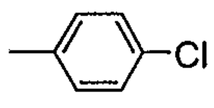
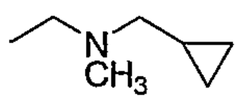
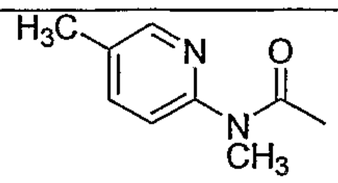
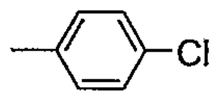
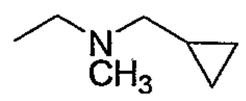
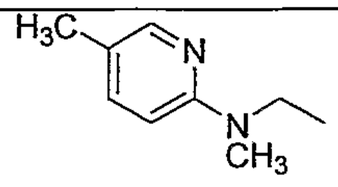
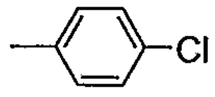
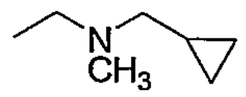
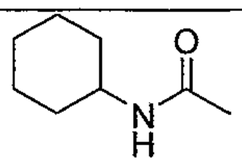
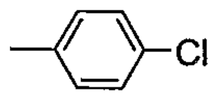
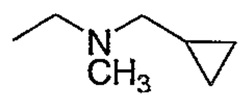
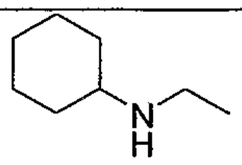
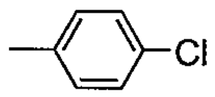
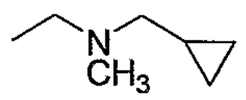
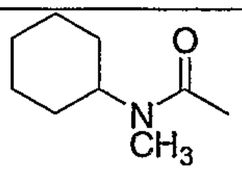
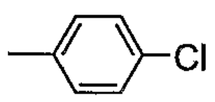
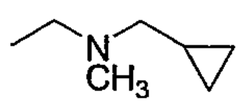
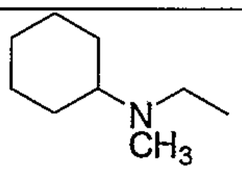
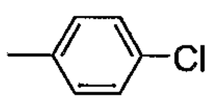
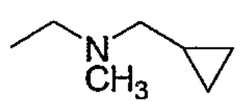
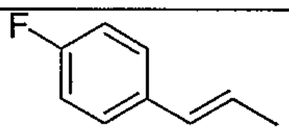
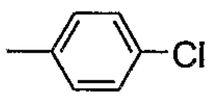
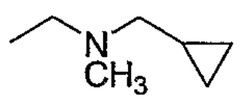
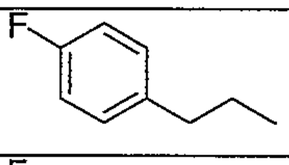
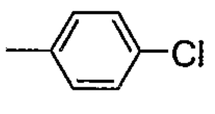
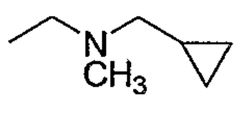
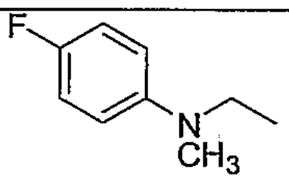
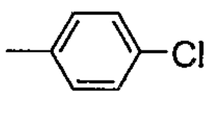
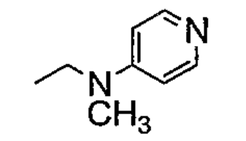
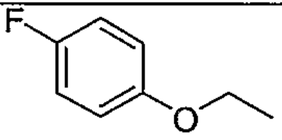
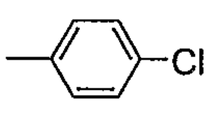
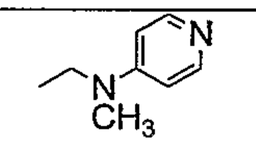
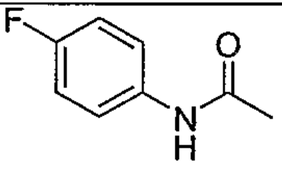
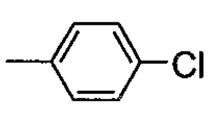
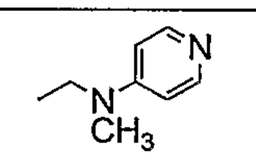
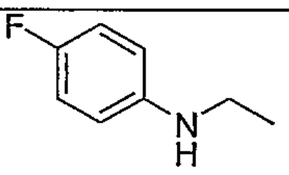
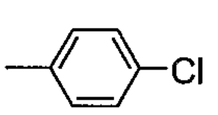
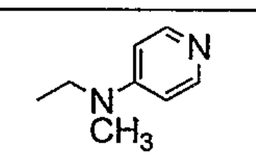
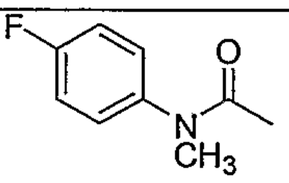
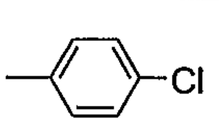
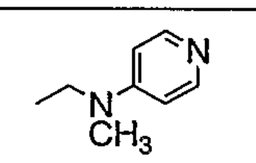
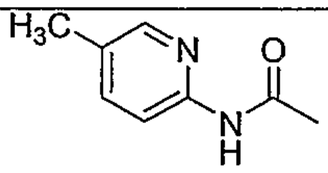
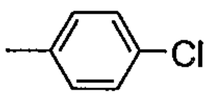
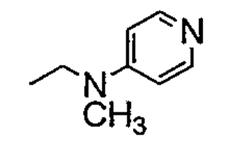
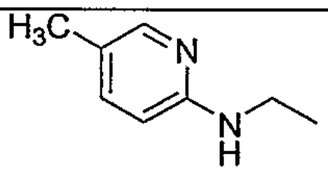
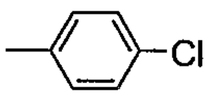
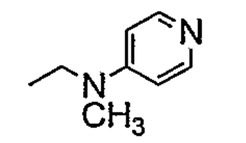
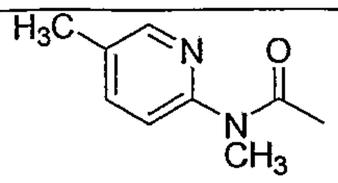
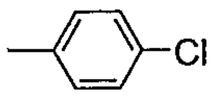
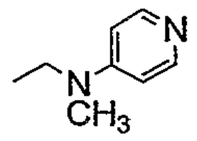
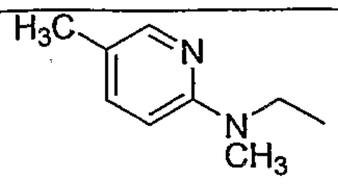
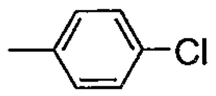
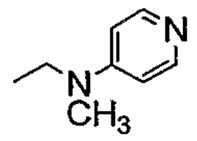
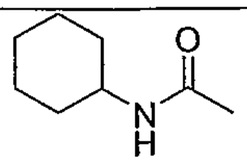
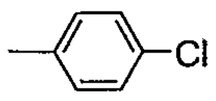
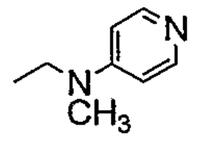
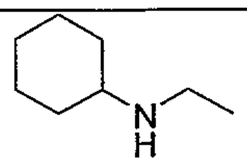
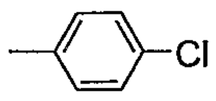
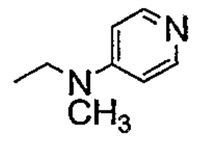
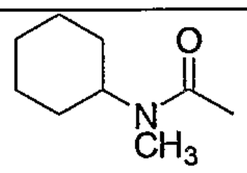
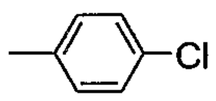
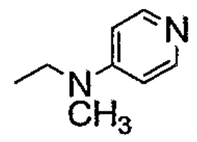
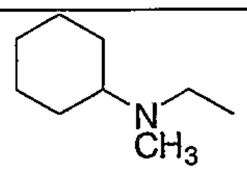
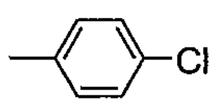
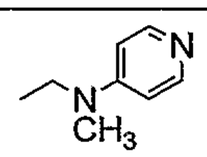
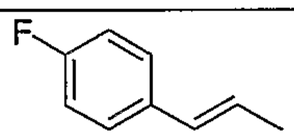
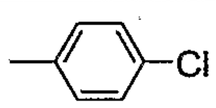
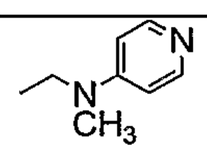
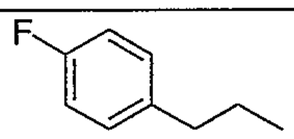
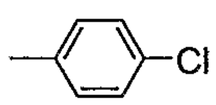
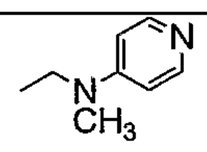
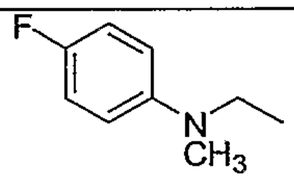
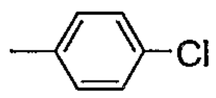
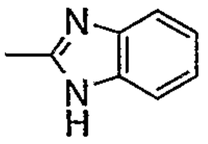
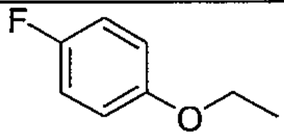
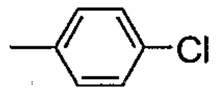
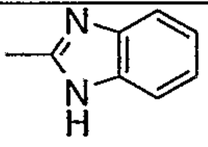
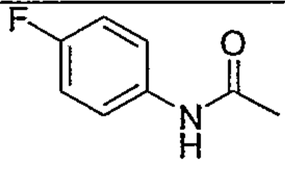
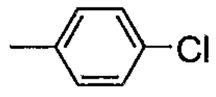
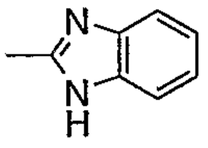
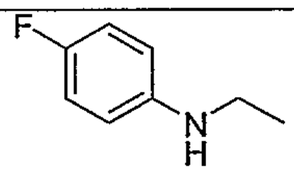
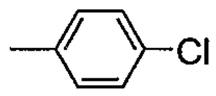
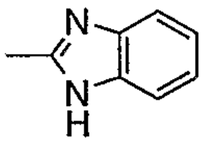
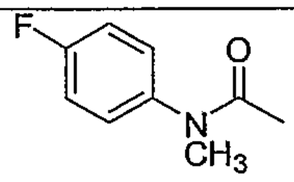
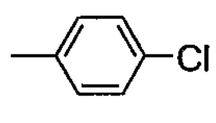
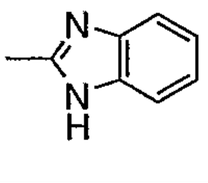
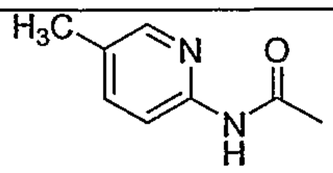
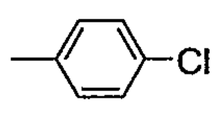
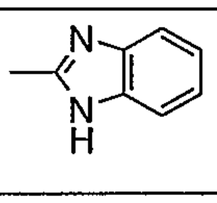
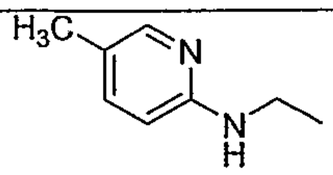
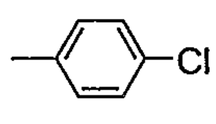
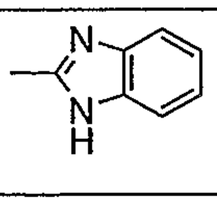
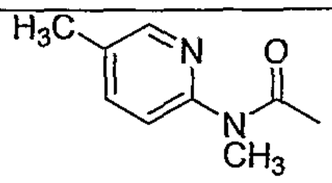
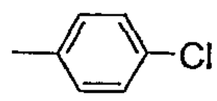
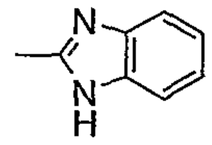
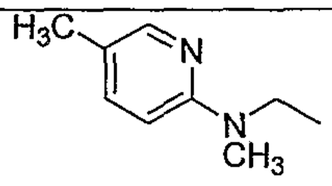
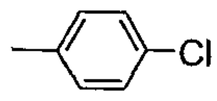
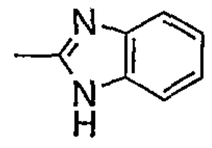
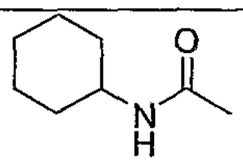
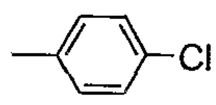
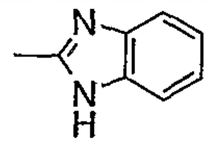
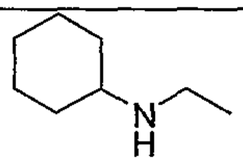
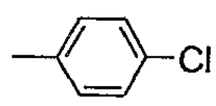
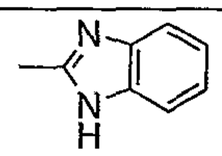
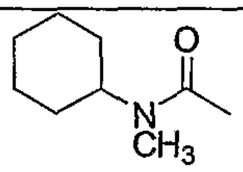
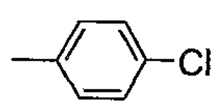
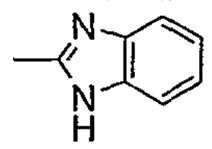
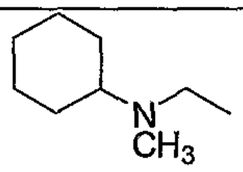
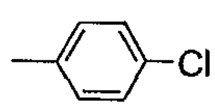
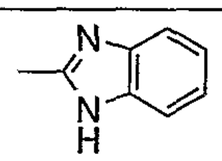
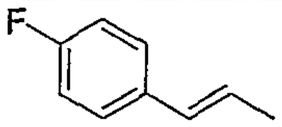
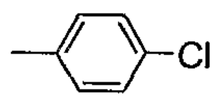
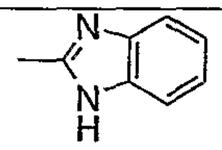
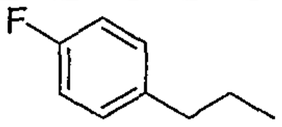
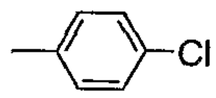
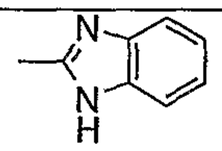
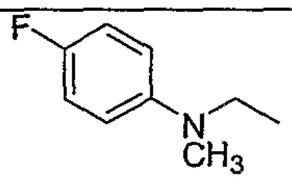
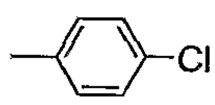
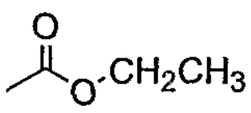
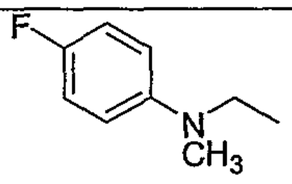
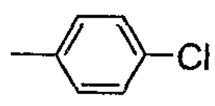
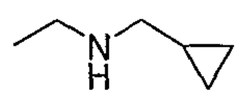
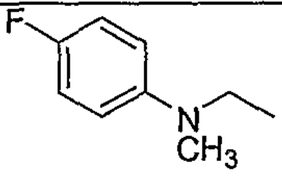
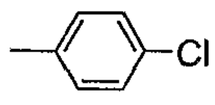
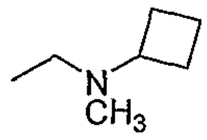
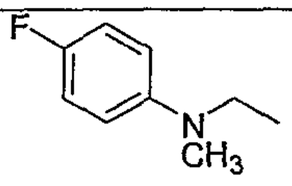
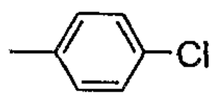
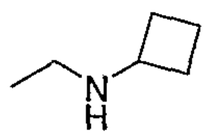
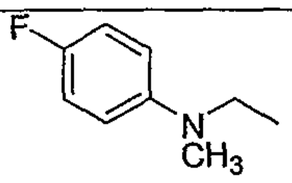
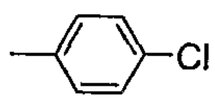
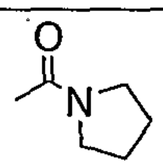
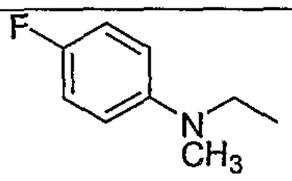
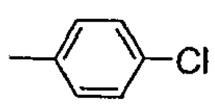
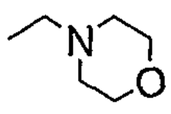
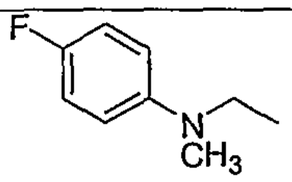
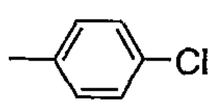
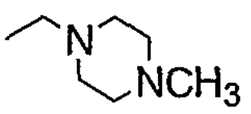
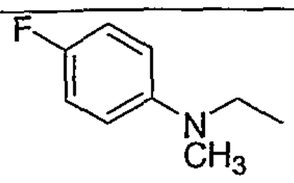
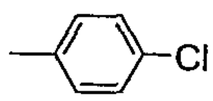
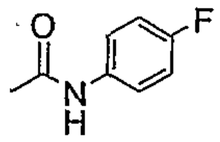
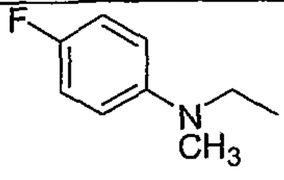
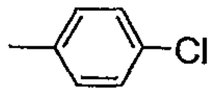
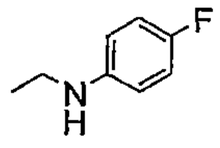
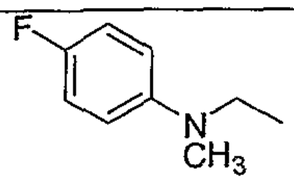
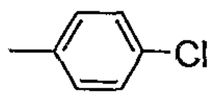
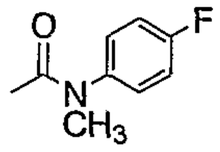
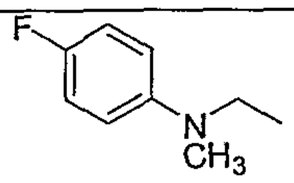
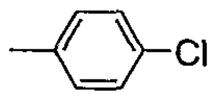
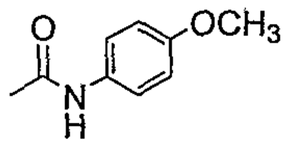
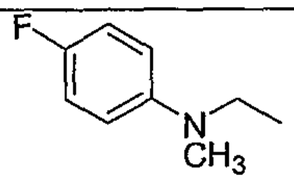
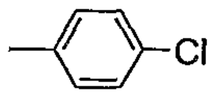
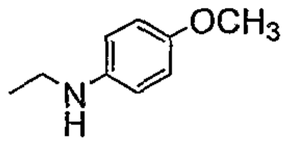
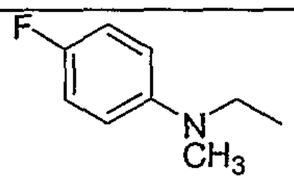
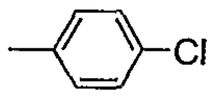
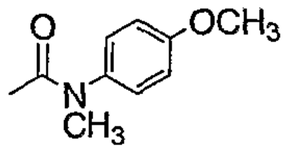
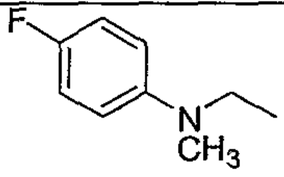
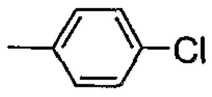
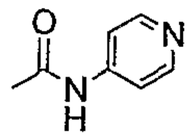
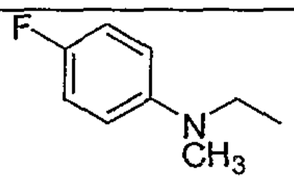
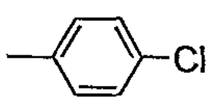
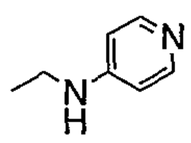
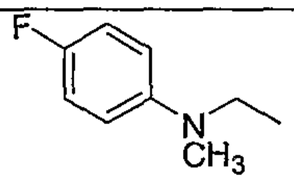
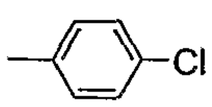
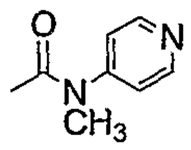
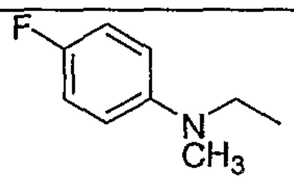
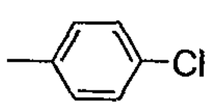
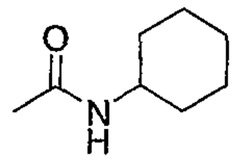
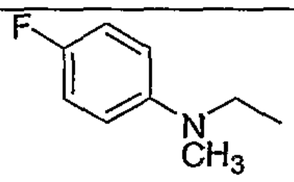
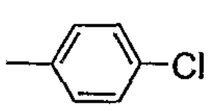
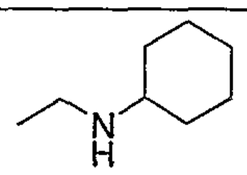
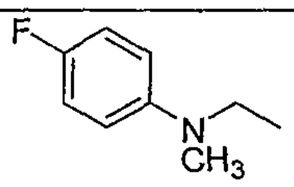
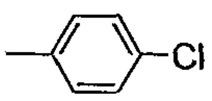
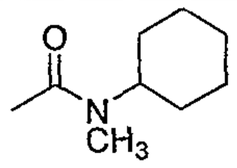
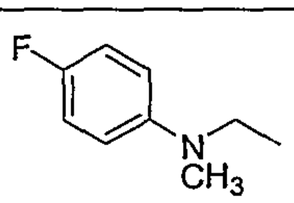
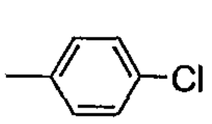
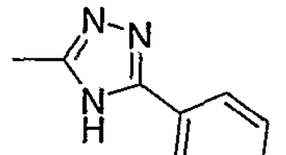
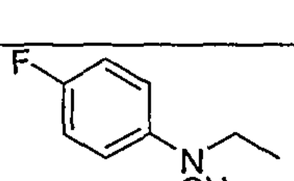
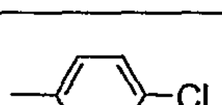
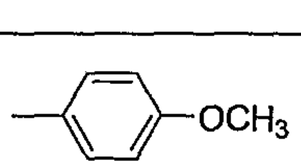
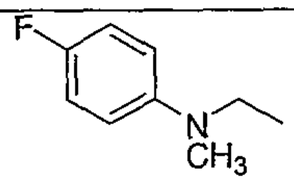
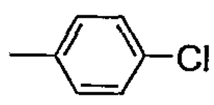
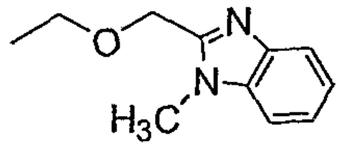
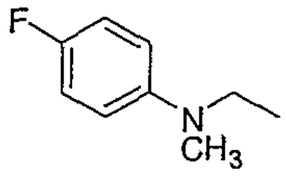
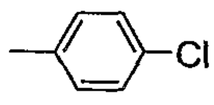
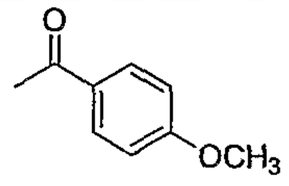
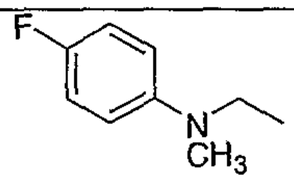
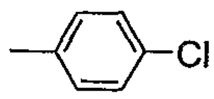
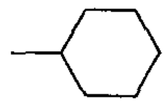
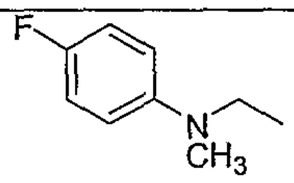
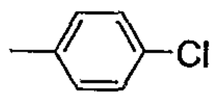
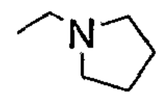
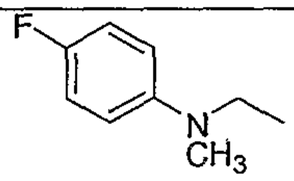
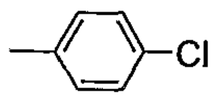
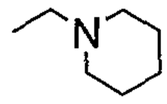
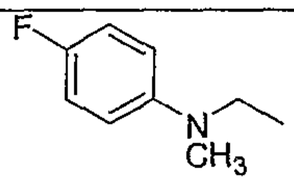
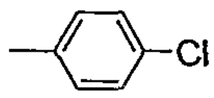
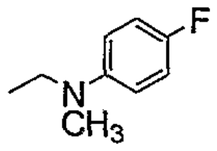
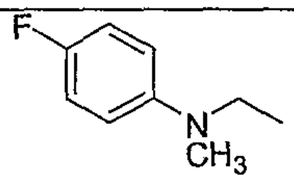
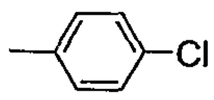
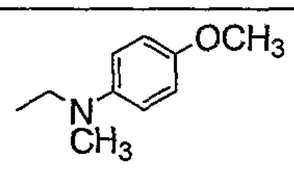
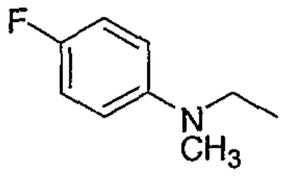
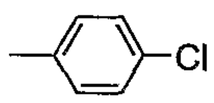
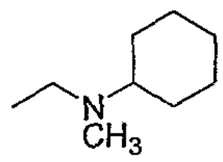
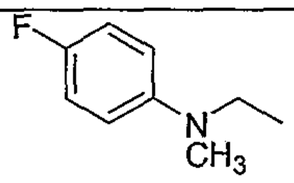
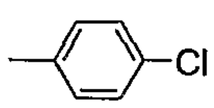
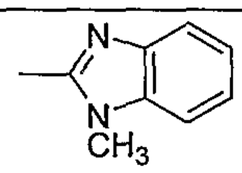
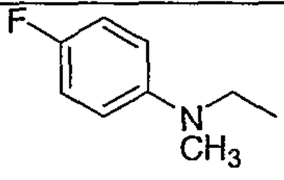
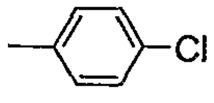
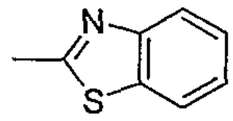
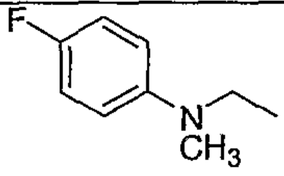
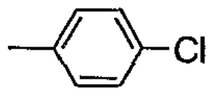
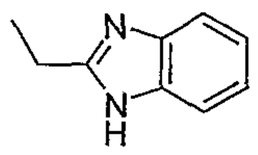
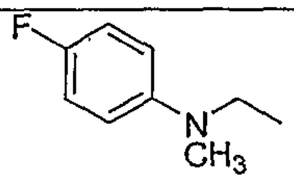
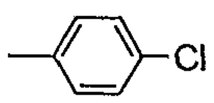
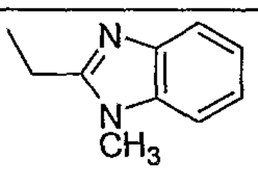
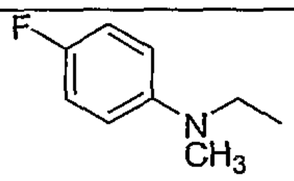
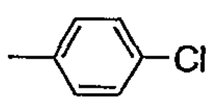
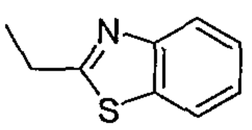
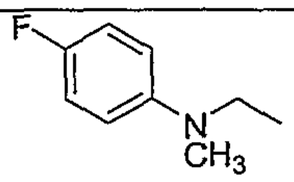
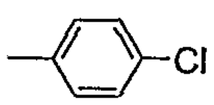
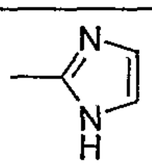
H-258			
H-259			
H-260			
H-261			
H-262			
H-263			
H-264			

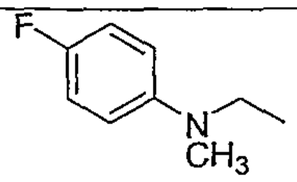
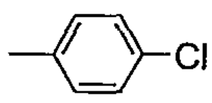
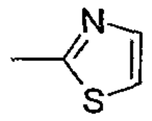
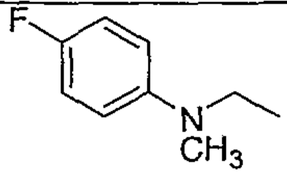
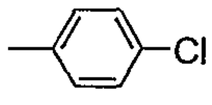
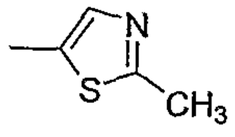
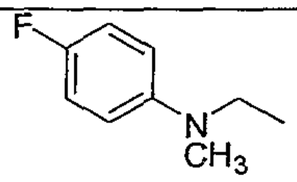
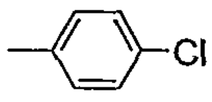
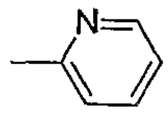
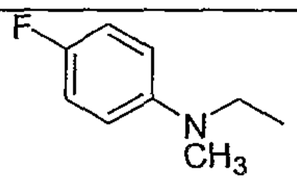
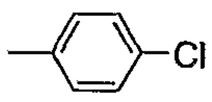
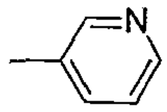
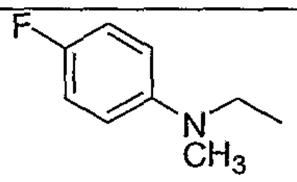
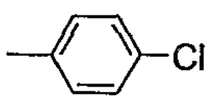
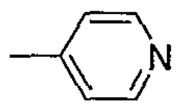
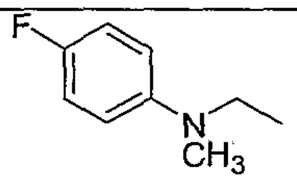
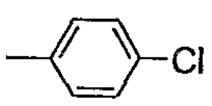
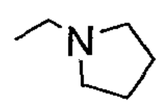
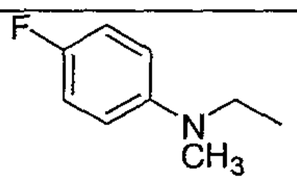
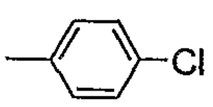
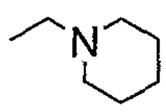
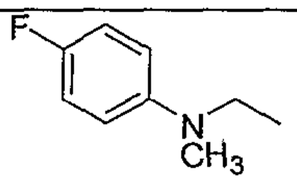
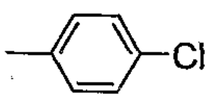
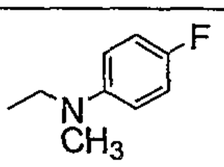
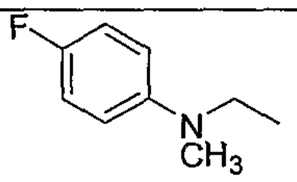
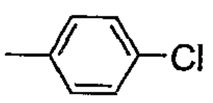
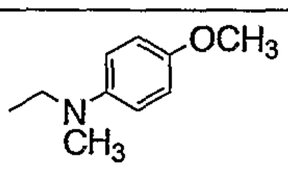
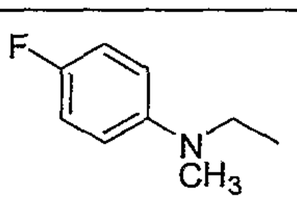
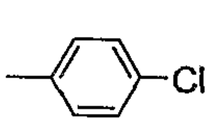
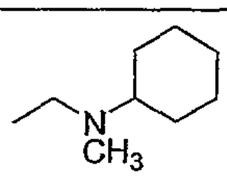
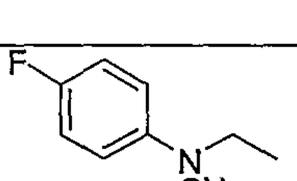
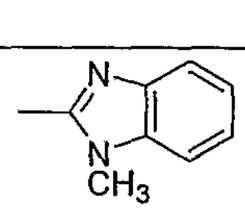
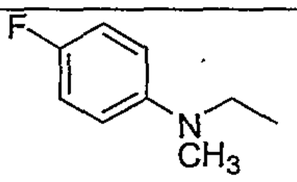
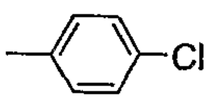
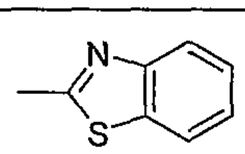
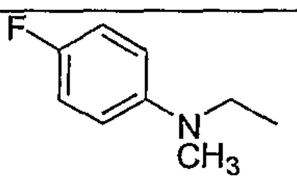
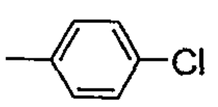
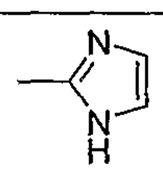
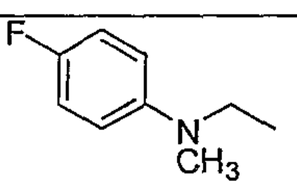
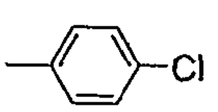
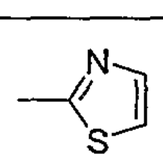
H-265			
H-266			
H-267			
H-268			
H-269			
H-270			
H-271			
H-272			
H-273			
H-274			
H-275			
H-276			
H-277			
H-278			
H-279			

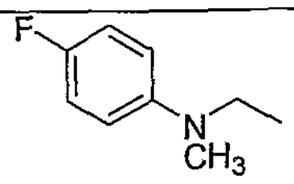
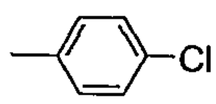
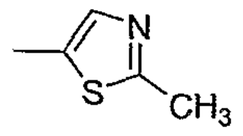
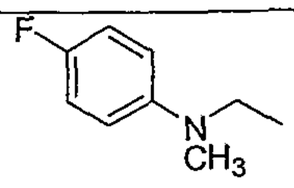
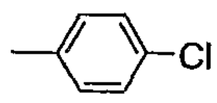
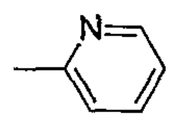
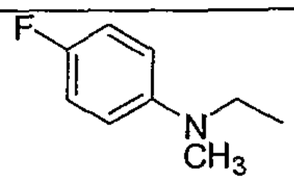
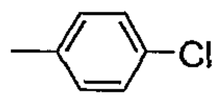
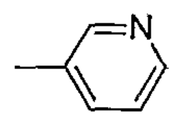
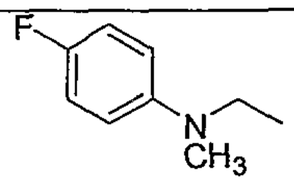
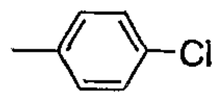
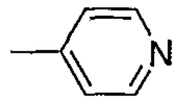
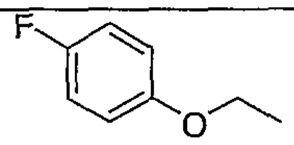
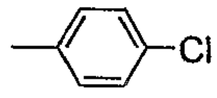
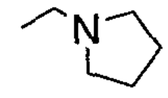
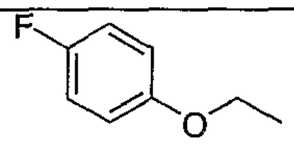
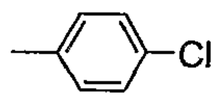
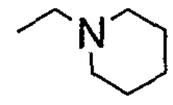
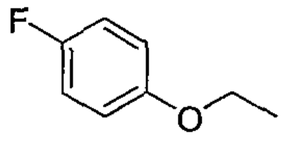
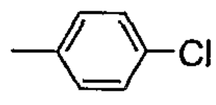
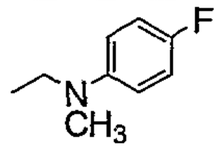
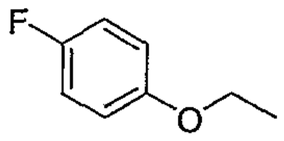
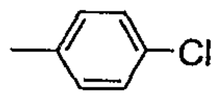
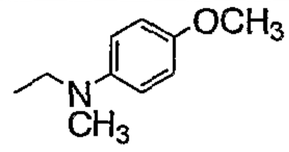
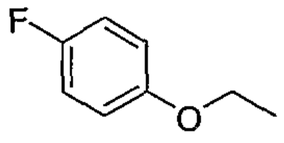
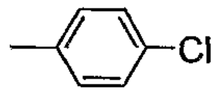
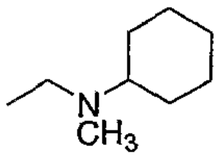
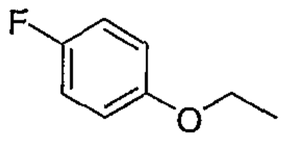
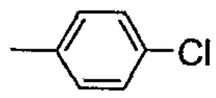
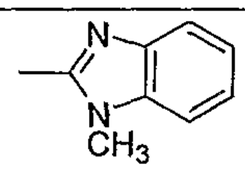
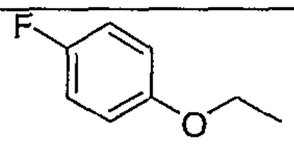
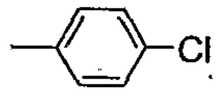
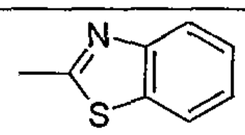
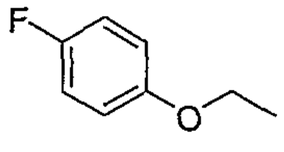
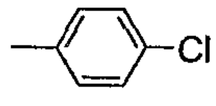
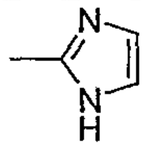
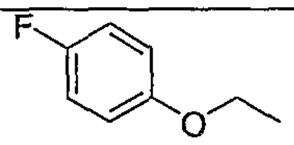
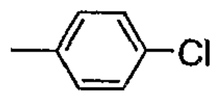
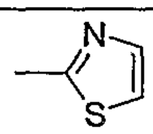
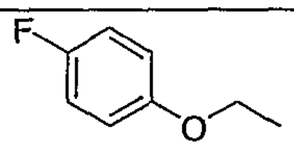
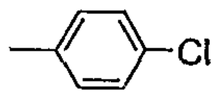
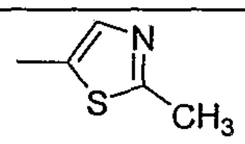
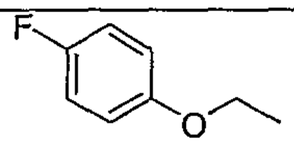
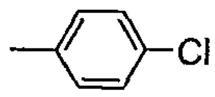
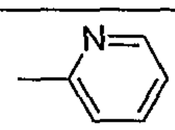
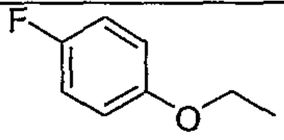
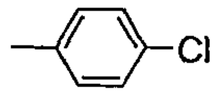
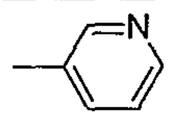
H-280			
H-281			
H-282			
H-283			
H-284			
H-285			
H-286			
H-287			
H-288			
H-289			
H-290			
H-291			
H-292			
H-293			
H-294			

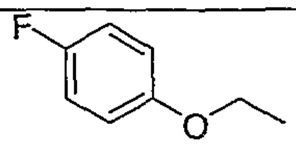
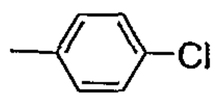
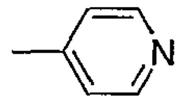
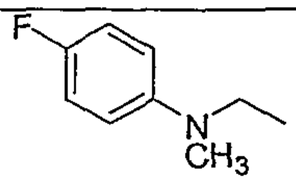
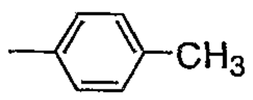
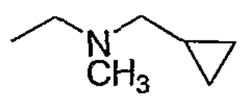
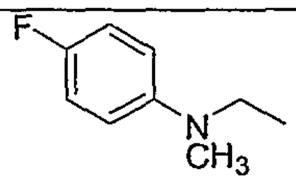
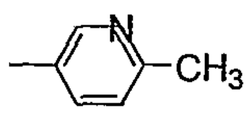
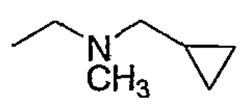
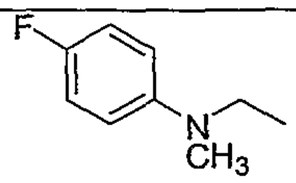
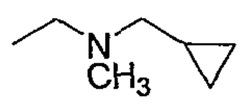
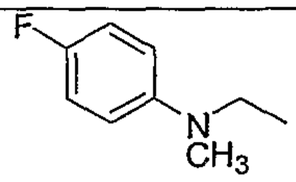
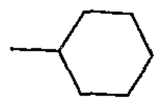
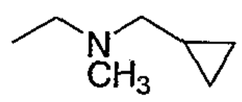
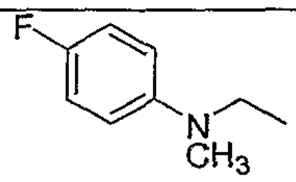
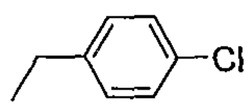
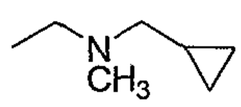
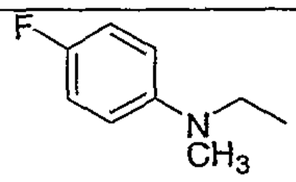
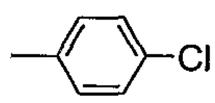
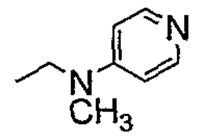
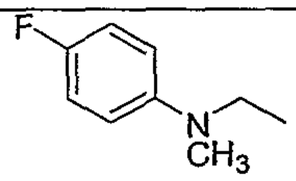
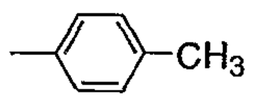
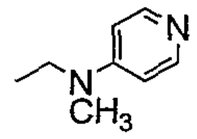
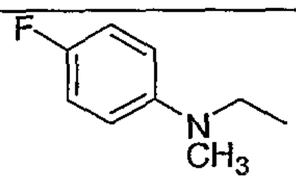
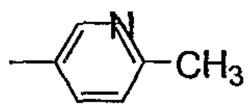
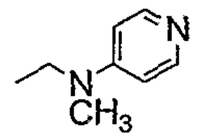
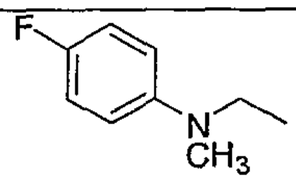
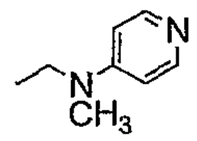
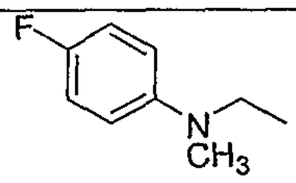
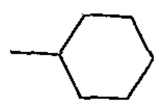
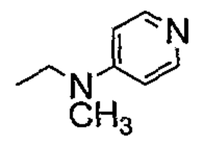
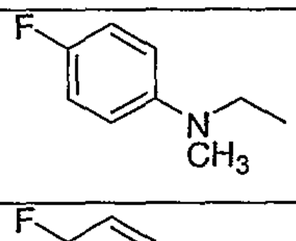
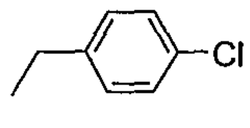
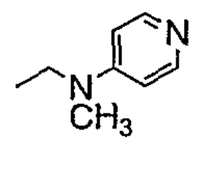
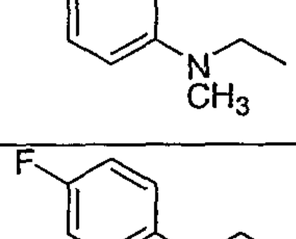
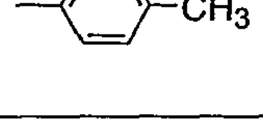
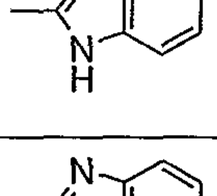
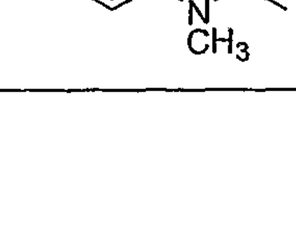
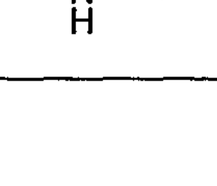
H-295			
H-296			
H-297			
H-298			
H-299			
H-300			
H-301			
H-302			
H-303			
H-304			
H-305			
H-306			
H-307			
H-308			
H-309			

H-310			
H-311			
H-312			
H-313			
H-314			
H-315			
H-316			
H-317			
H-318			
H-319			
H-320			
H-321			
H-322			
H-323			

H-324			
H-325			
H-326			
H-327			
H-328			
H-329			
H-330			
H-331			
H-332			
H-333			
H-334			
H-335			
H-336			
H-337			

H-338			
H-339			
H-340			
H-341			
H-342			
H-343			
H-344			
H-345			
H-346			
H-347			
H-348			
H-349			
H-350			
H-351			

H-352			
H-353			
H-354			
H-355			
H-356			
H-357			
H-358			
H-359			
H-360			
H-361			
H-362			
H-363			
H-364			
H-365			
H-366			
H-367			

H-368			
H-369			
H-370			
H-371		CH_3	
H-372			
H-373			
H-374			
H-375			
H-376			
H-377		CH_3	
H-378			
H-379			
H-380			
H-381			

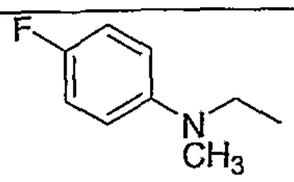
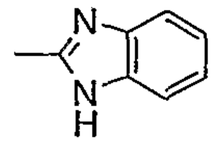
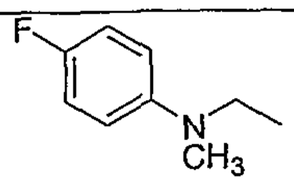
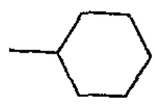
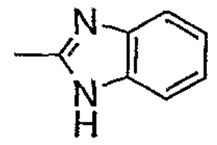
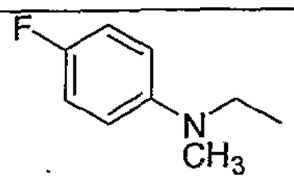
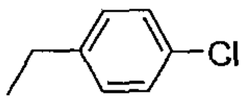
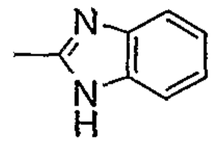
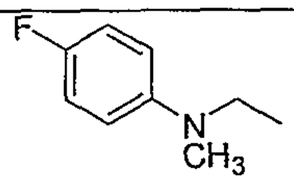
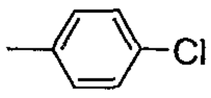
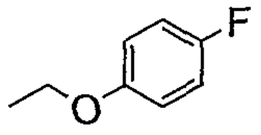
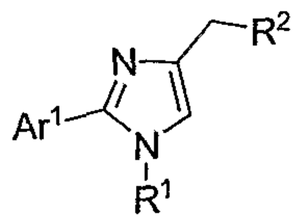
H-382		CH_3	
H-383			
H-384			
H385			

TABLE J-1A



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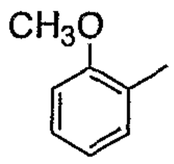
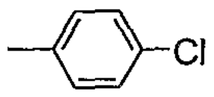
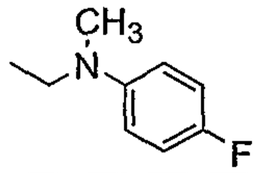
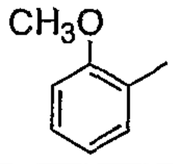
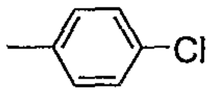
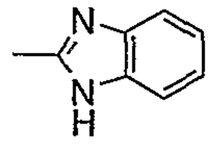
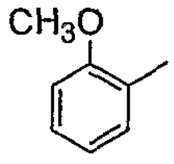
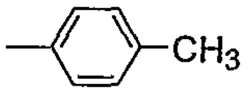
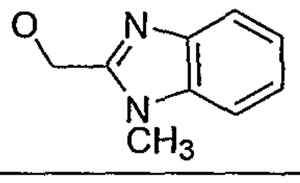
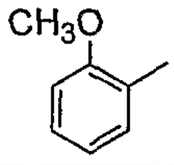
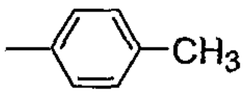
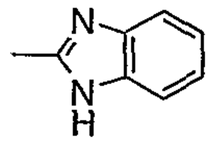
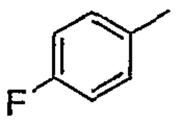
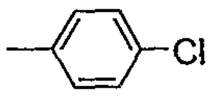
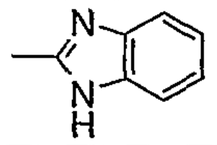
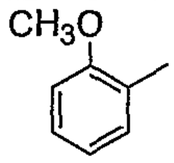
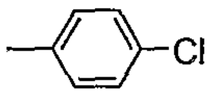
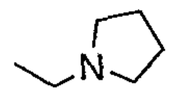
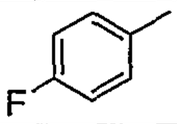
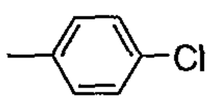
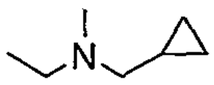
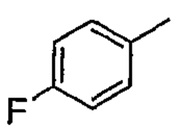
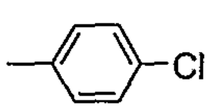
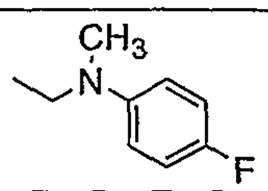
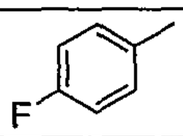
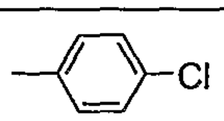
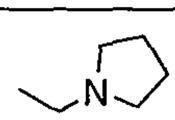
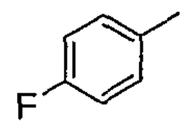
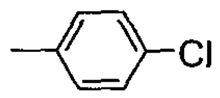
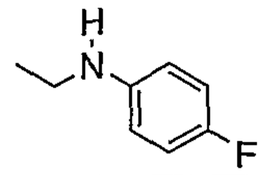
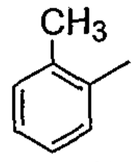
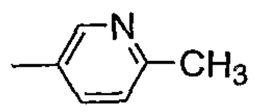
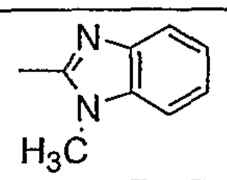
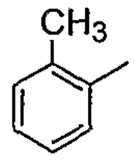
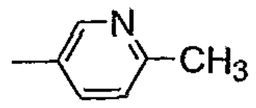
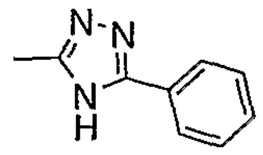
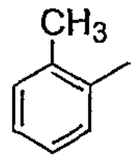
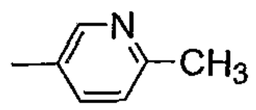
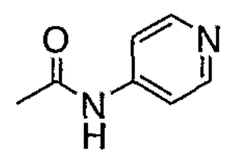
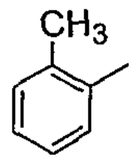
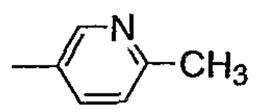
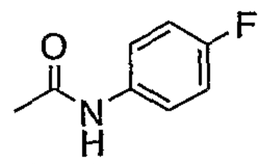
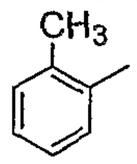
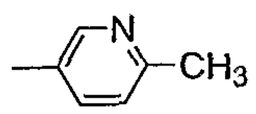
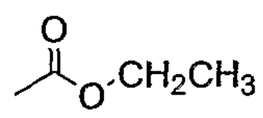
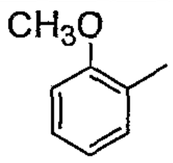
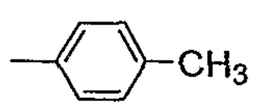
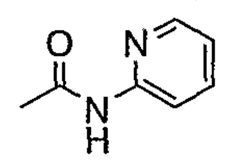
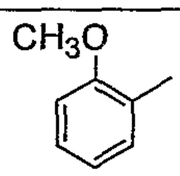
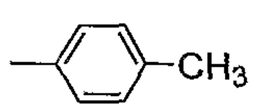
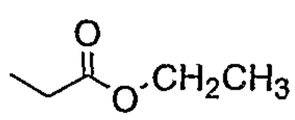
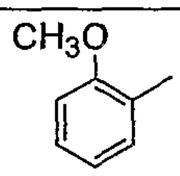
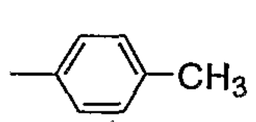
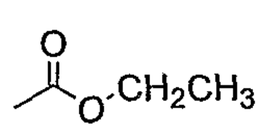
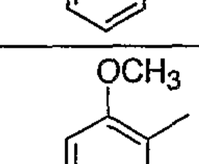
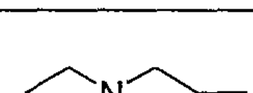
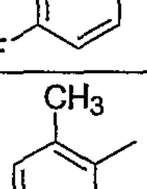
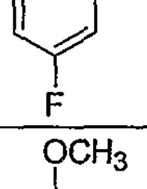
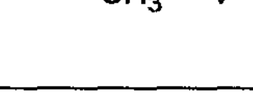
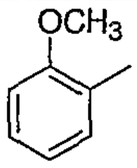
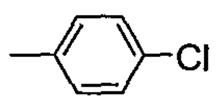
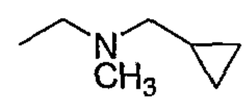
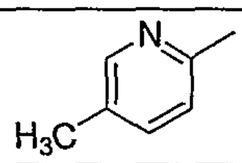
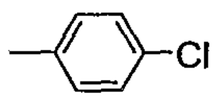
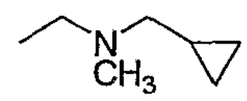
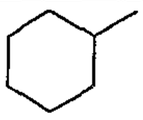
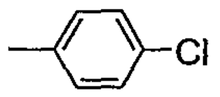
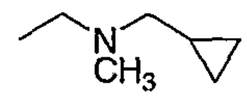
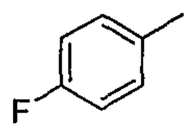
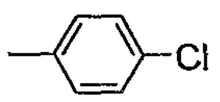
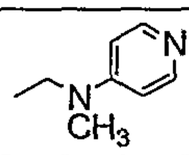
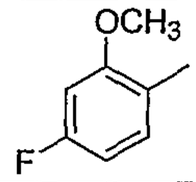
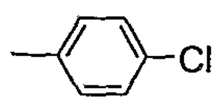
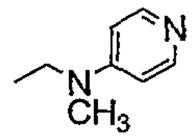
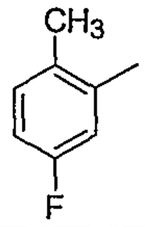
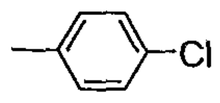
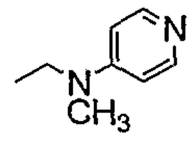
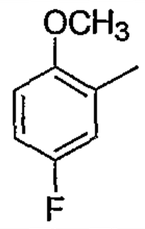
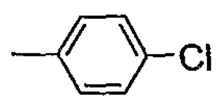
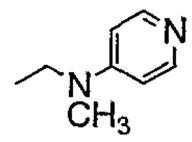
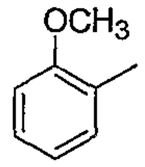
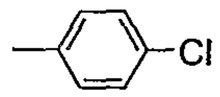
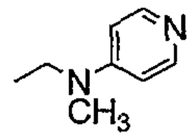
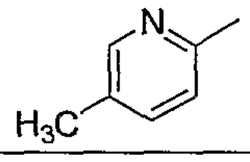
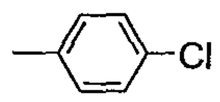
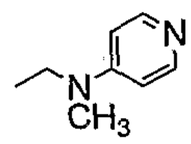
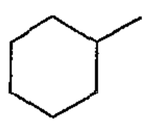
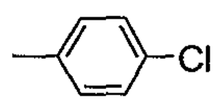
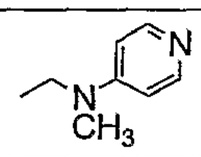
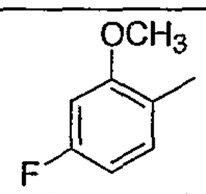
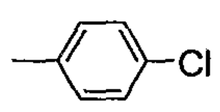
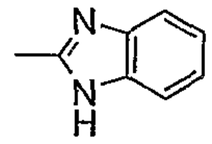
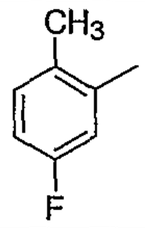
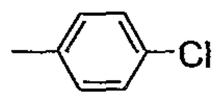
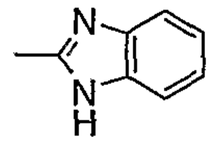
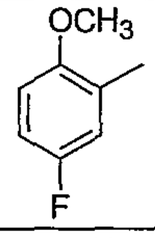
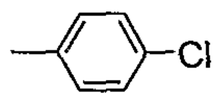
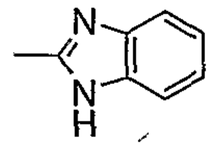
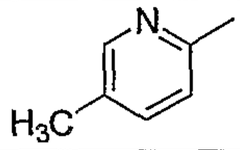
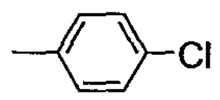
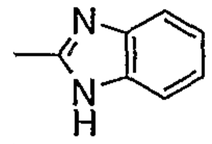
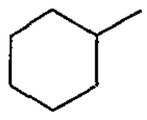
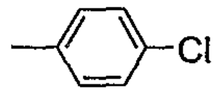
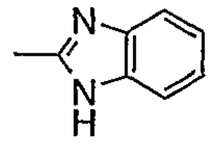
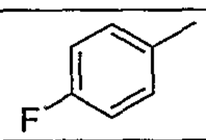
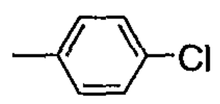
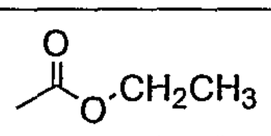
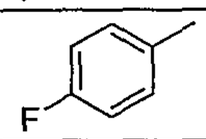
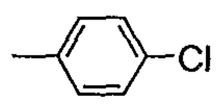
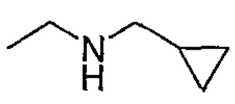
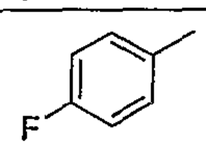
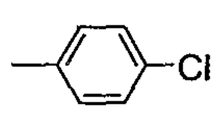
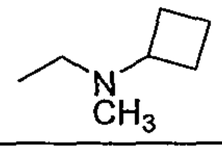
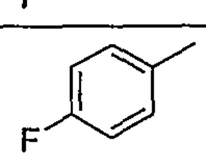
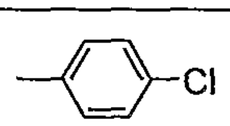
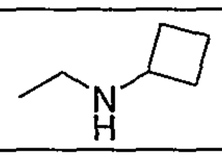
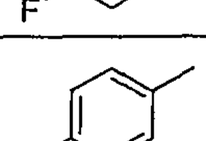
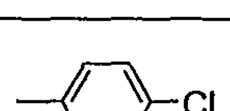
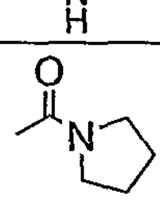
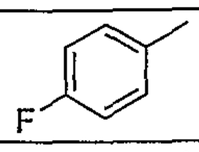
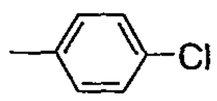
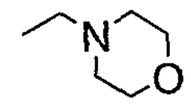
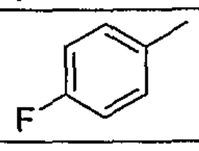
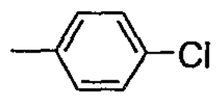
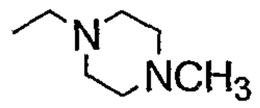
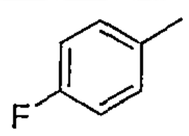
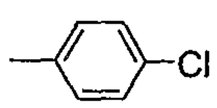
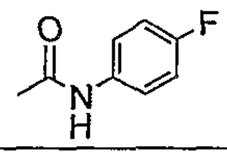
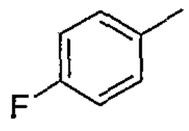
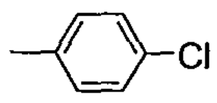
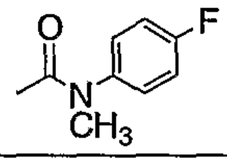
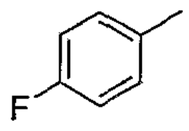
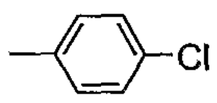
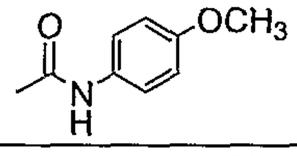
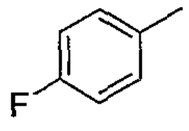
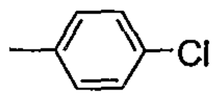
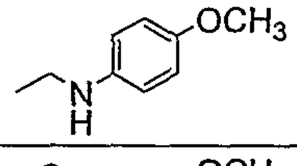
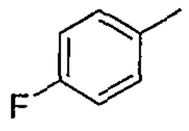
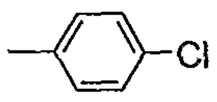
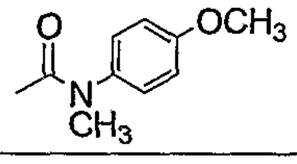
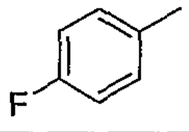
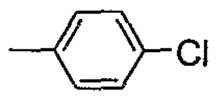
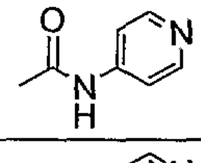
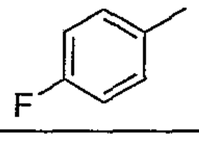
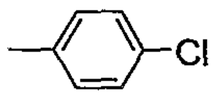
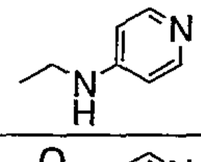
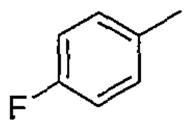
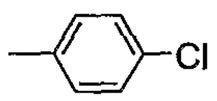
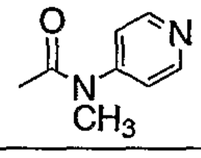
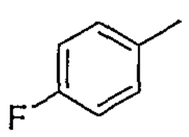
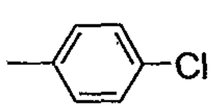
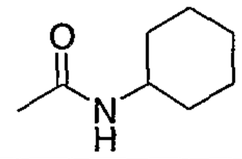
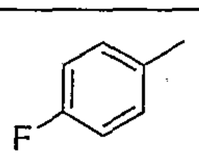
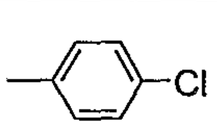
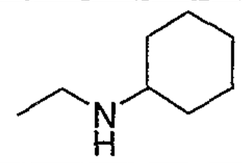
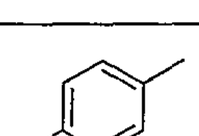
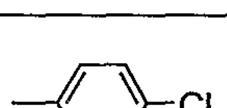
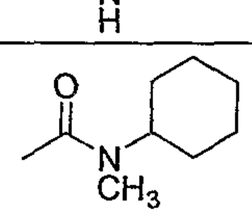
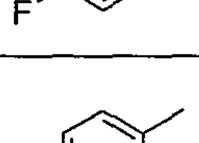
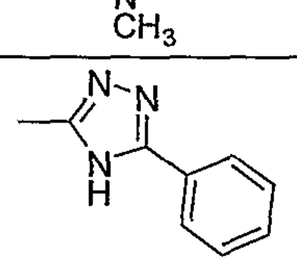
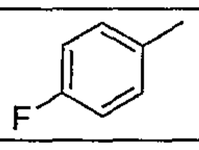
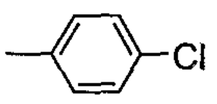
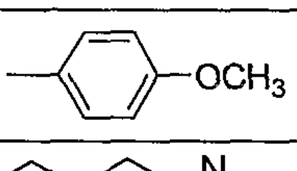
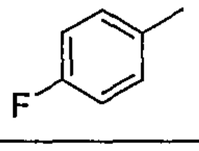
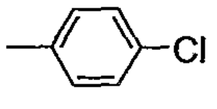
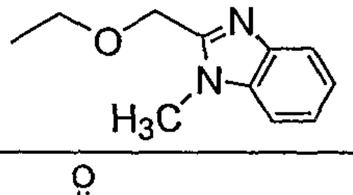
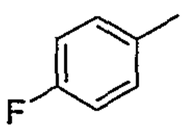
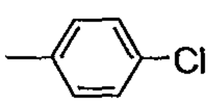
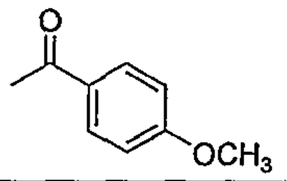
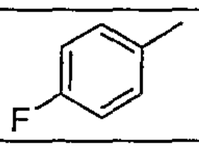
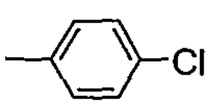
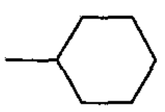
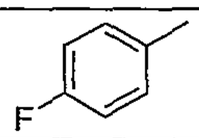
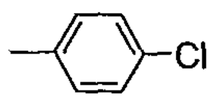
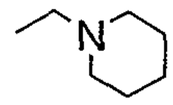
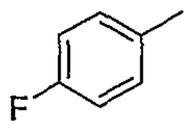
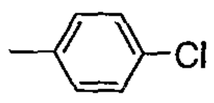
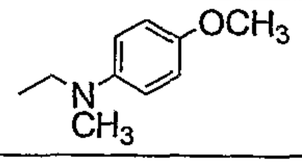
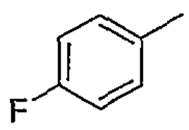
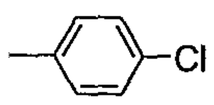
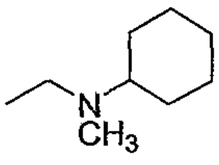
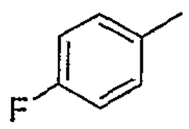
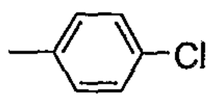
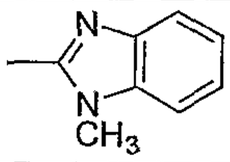
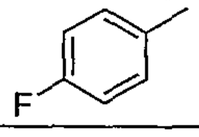
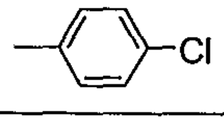
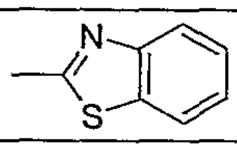
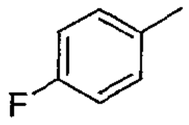
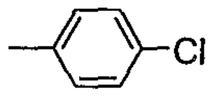
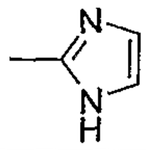
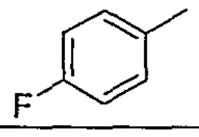
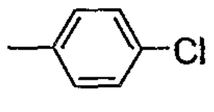
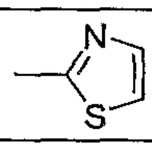
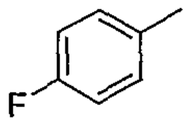
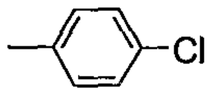
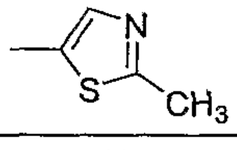
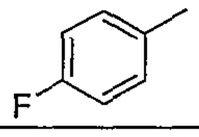
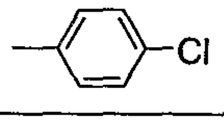
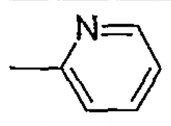
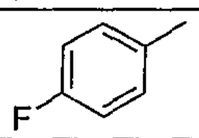
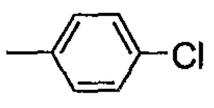
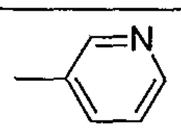
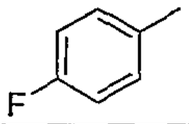
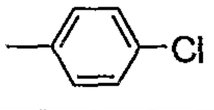
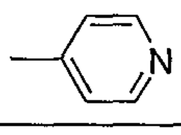
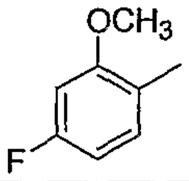
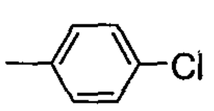
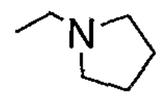
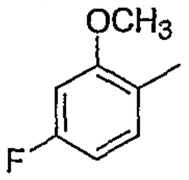
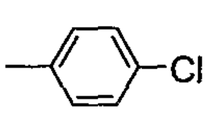
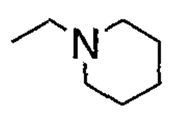
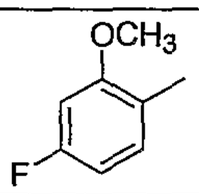
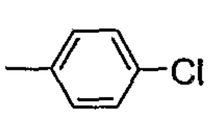
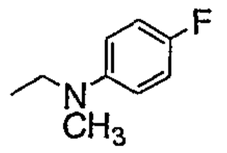
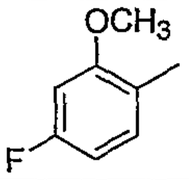
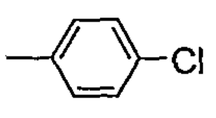
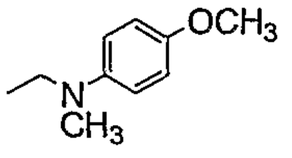
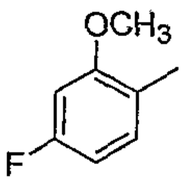
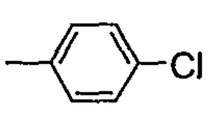
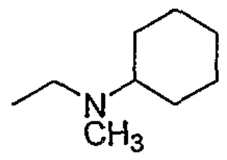
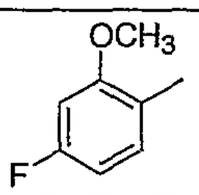
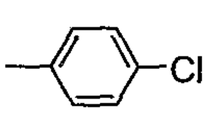
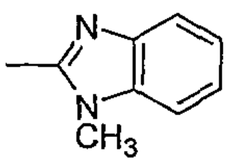
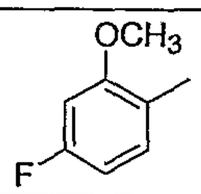
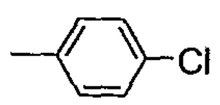
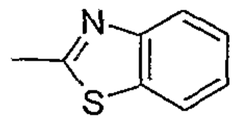
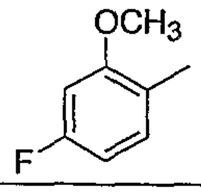
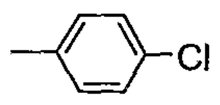
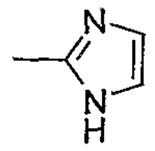
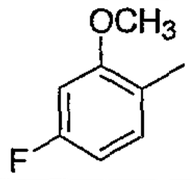
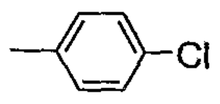
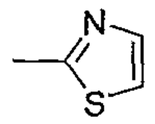
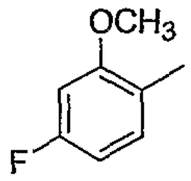
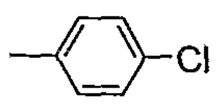
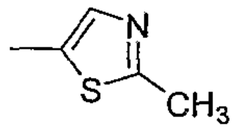
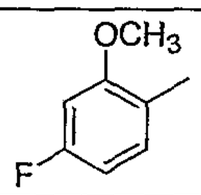
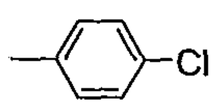
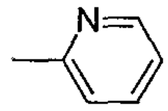
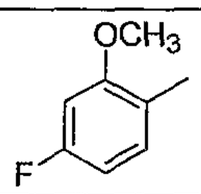
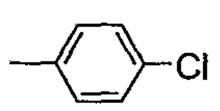
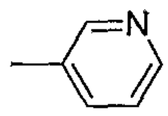
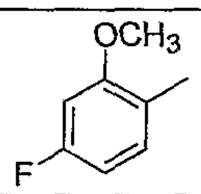
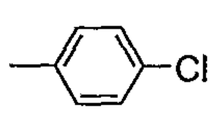
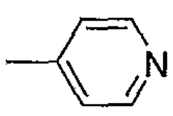
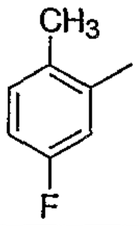
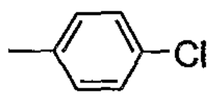
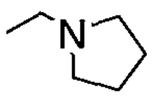
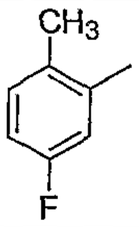
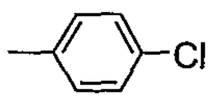
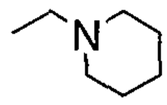
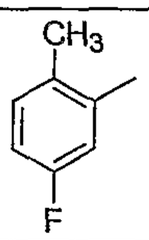
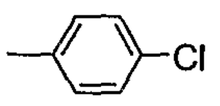
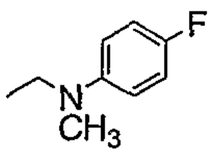
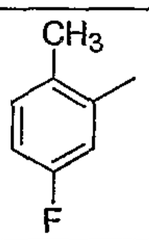
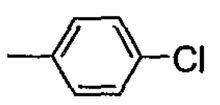
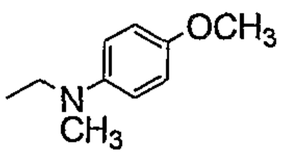
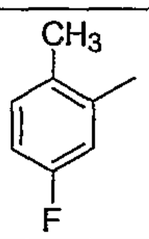
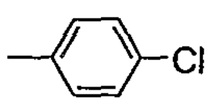
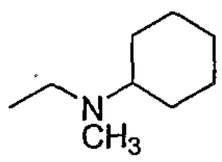
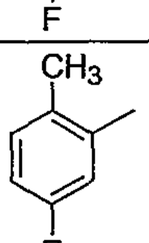
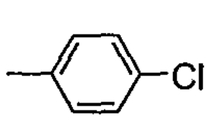
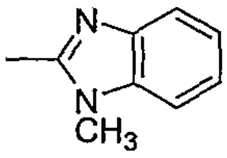
J-1			
J-2			
J-3			
J-4			
J-5			
J-6			
J-7			
J-8			
J-9			

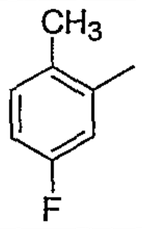
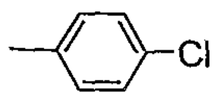
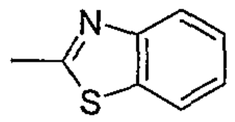
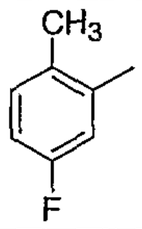
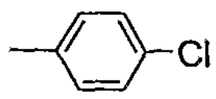
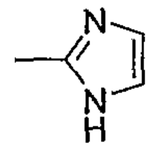
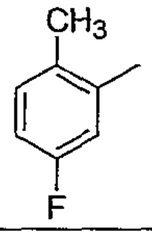
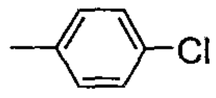
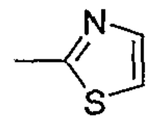
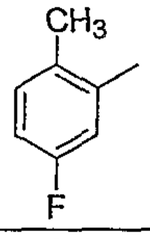
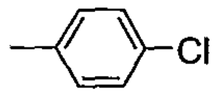
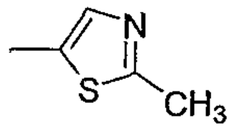
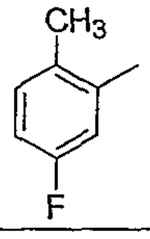
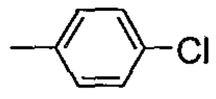
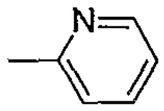
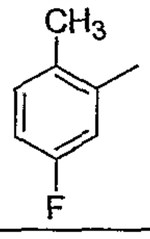
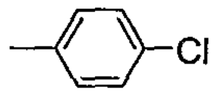
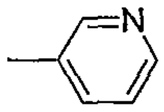
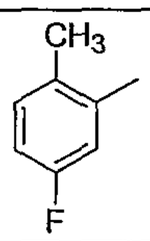
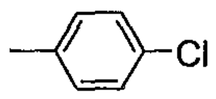
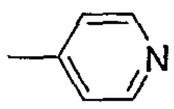
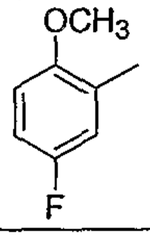
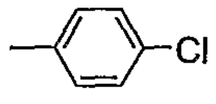
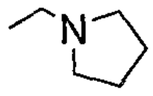
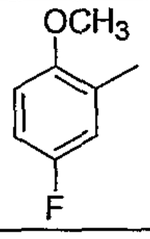
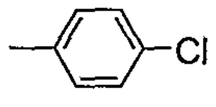
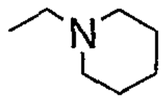
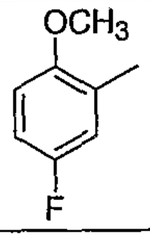
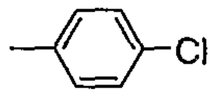
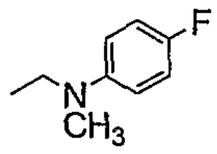
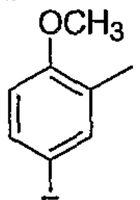
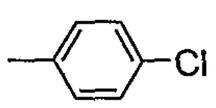
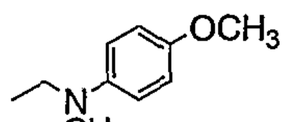
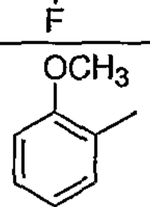
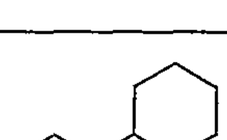
J-10			
J-11			
J-12			
J-13			
J-14			
J-15			
J-16			
J-17			
J-18			
J-19			
J-20			
J-21			
J-22			
J-23			
J-24			
J-25			

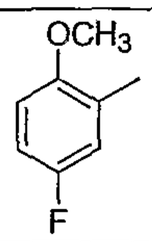
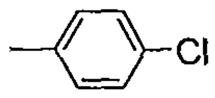
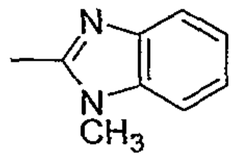
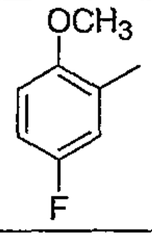
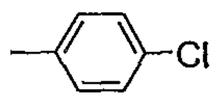
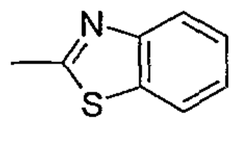
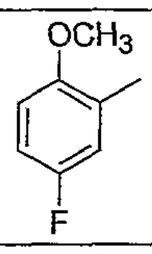
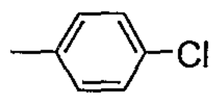
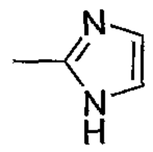
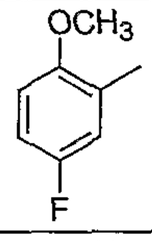
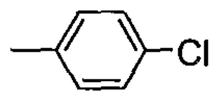
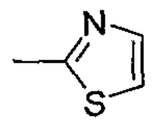
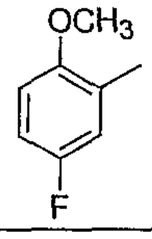
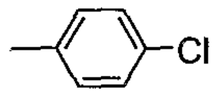
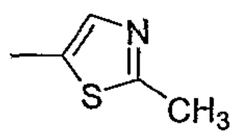
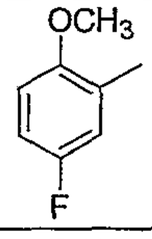
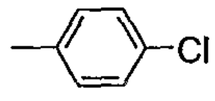
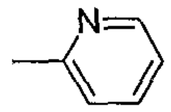
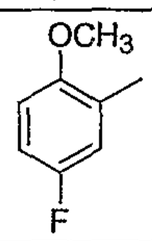
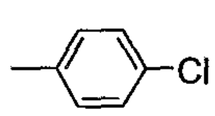
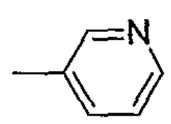
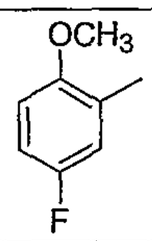
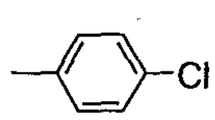
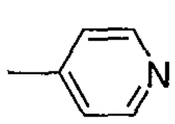
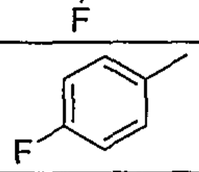
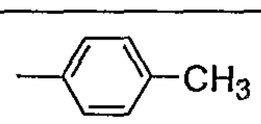
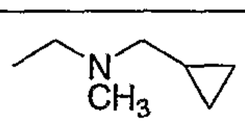
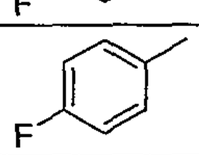
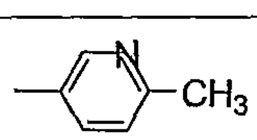
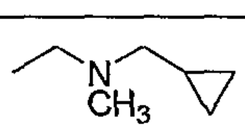
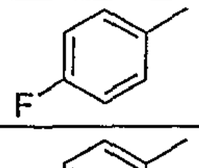
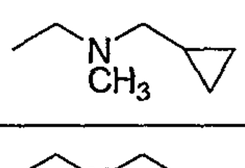
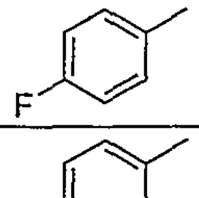
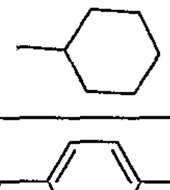
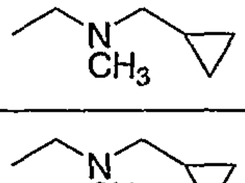
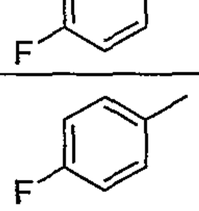
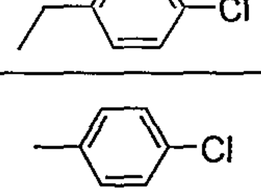
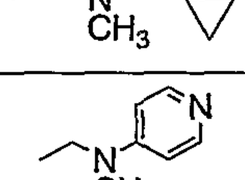
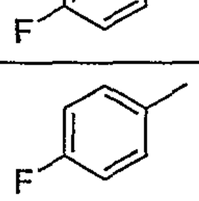
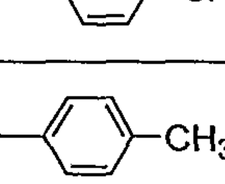
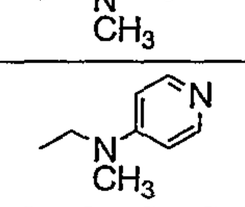
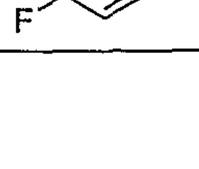
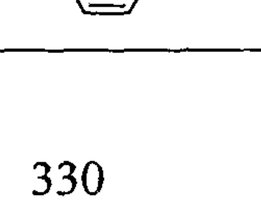
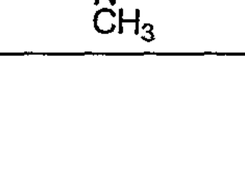
J-26			
J-27			
J-28			
J-29			
J-30			
J-31			
J-32			
J-33			
J-34			
J-35			
J-36			
J-37			
J-38			
J-39			
J-40			
J-41			

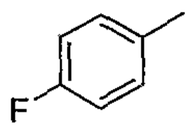
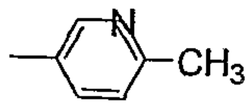
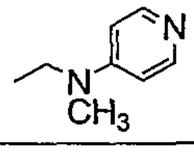
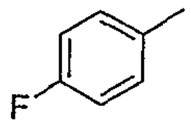
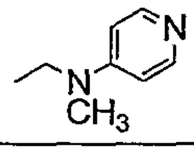
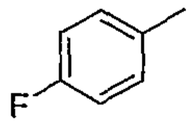
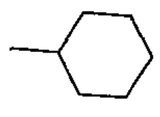
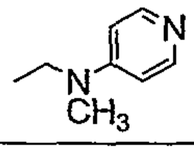
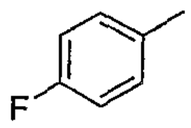
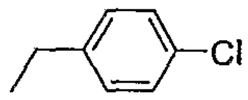
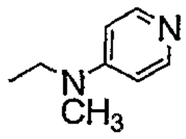
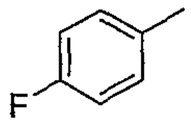
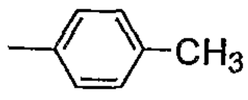
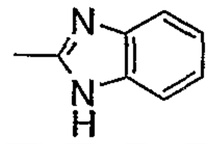
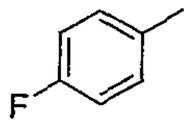
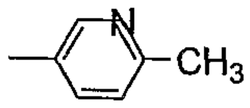
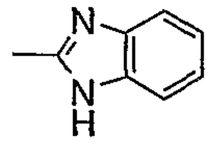
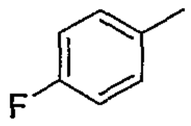
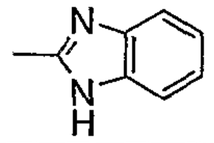
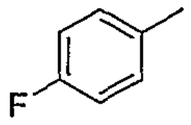
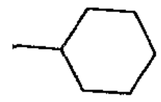
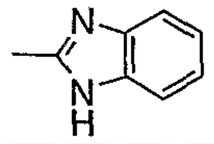
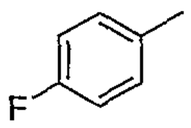
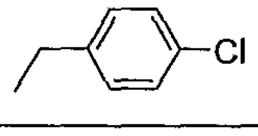
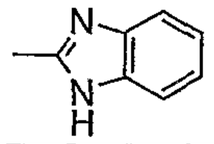
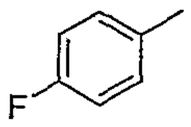
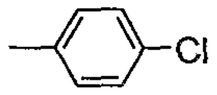
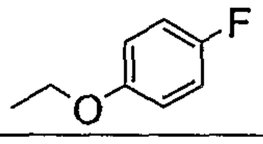
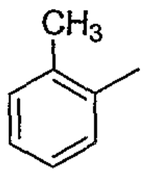
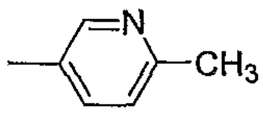
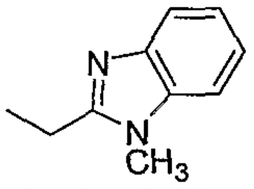
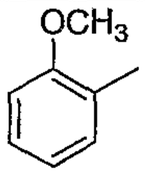
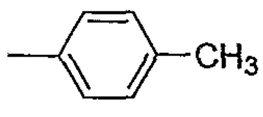
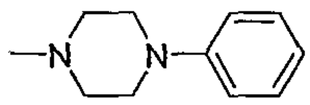
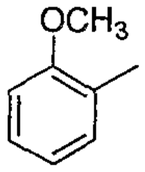
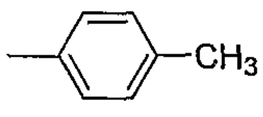
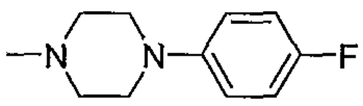
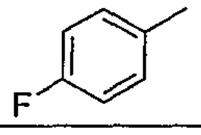
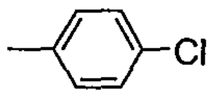
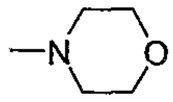
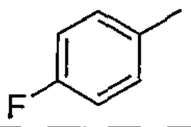
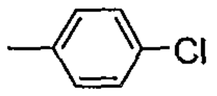
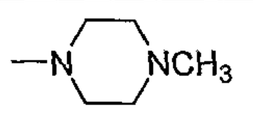
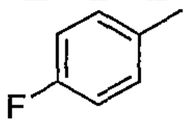
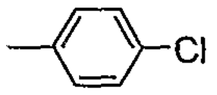
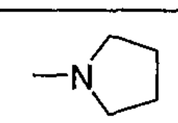
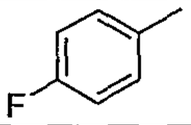
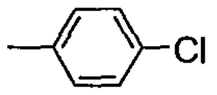
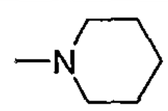
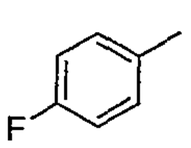
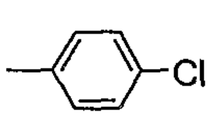
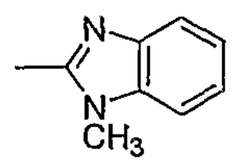
J-42			
J-43			
J-44			
J-45			
J-46			
J-47			
J-48			
J-49			
J-50			
J-51			
J-52			
J-53			
J-54			
J-55			
J-56			
J-57			
J-58			
J-59			

J-60			
J-61			
J-62			
J-63			
J-64			
J-65			
J-66			
J-67			
J-68			
J-69			
J-70			
J-71			
J-72			
J-73			
J-74			
J-75			
J-76			

J-77			
J-78			
J-79			
J-80			
J-81			
J-82			
J-83			
J-84			
J-85			
J-86			
J-87			
J-88			
J-89			

J-90			
J-91			
J-92			
J-93			
J-94			
J-95			
J-96			
J-97			
J-98			
J-99			
J-100			
J-101			

J-102			
J-103			
J-104			
J-105			
J-106			
J-107			
J-108			
J-109			
J-110			
J-111			
J-112		CH_3	
J-113			
J-114			
J-115			
J-116			

J-117			
J-118		CH_3	
J-119			
J-120			
J-121			
J-122			
J-123		CH_3	
J-124			
J-125			
J-126			
J-127			
J-128			
J-129			
J-130			
J-131			
J-132			
J-133			
J-134			

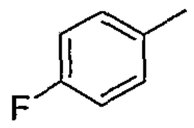
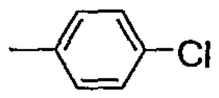
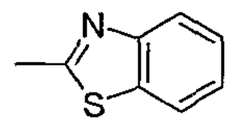
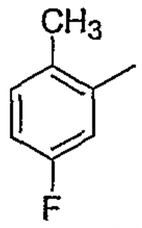
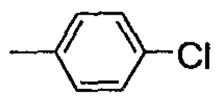
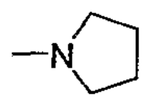
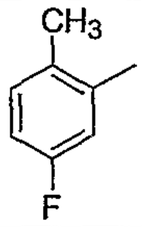
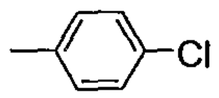
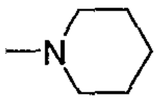
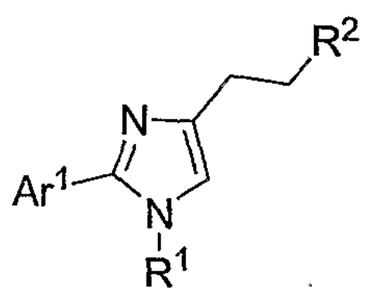
J-135			
J-136			
J-137			

Table J-1B



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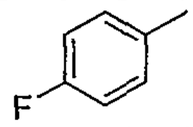
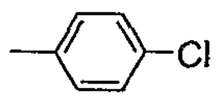
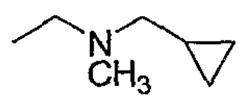
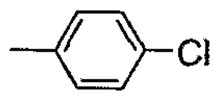
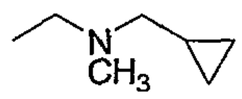
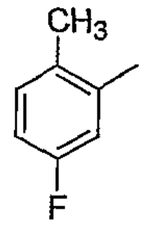
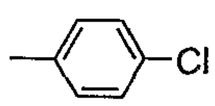
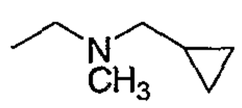
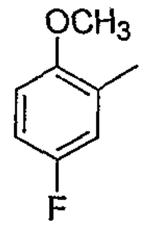
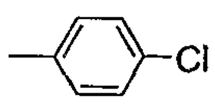
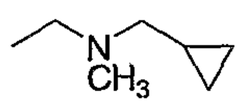
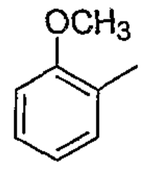
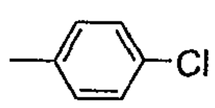
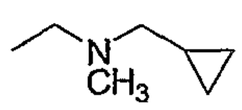
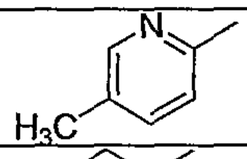
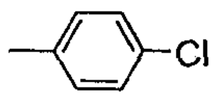
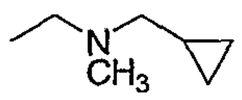
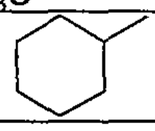
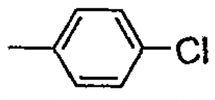
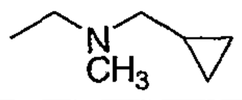
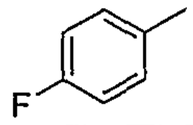
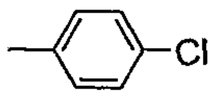
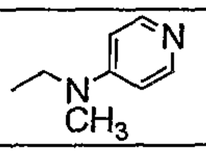
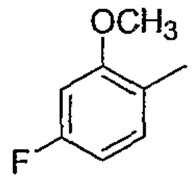
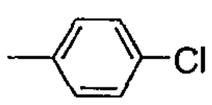
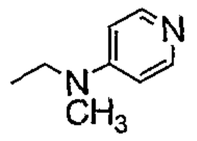
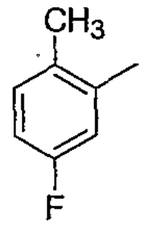
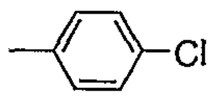
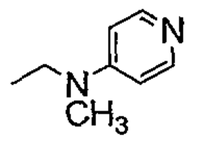
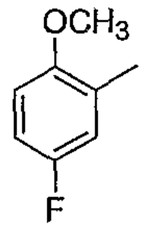
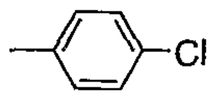
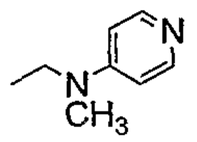
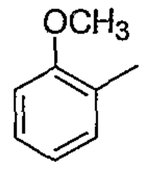
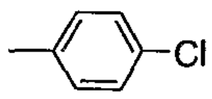
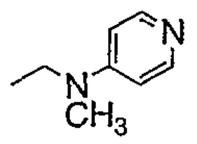
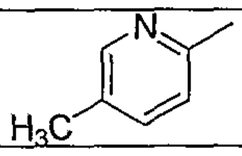
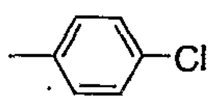
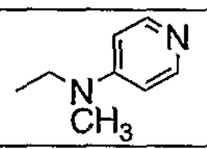
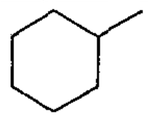
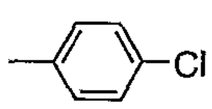
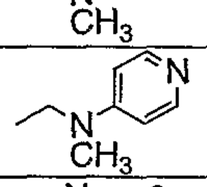
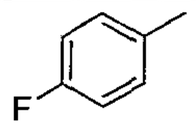
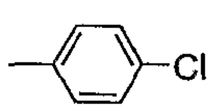
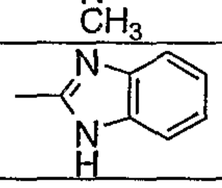
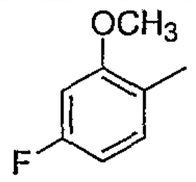
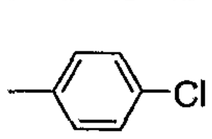
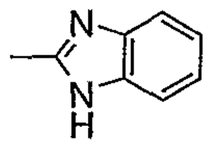
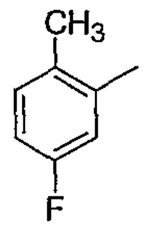
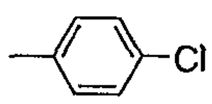
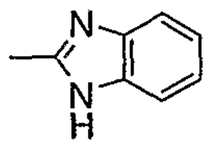
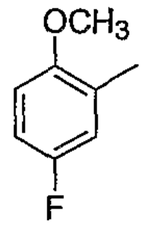
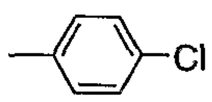
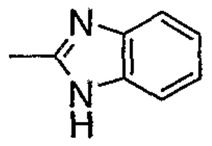
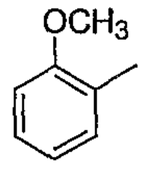
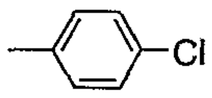
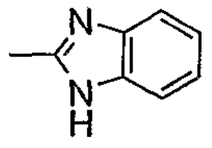
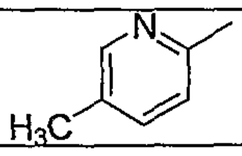
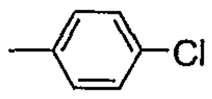
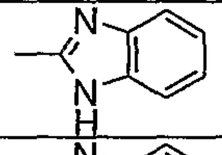
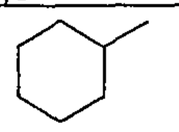
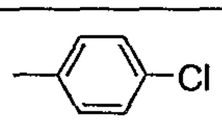
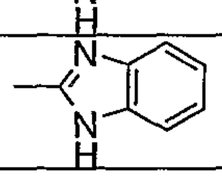
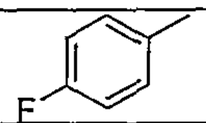
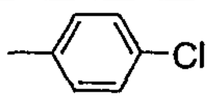
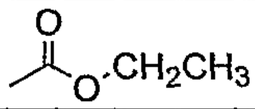
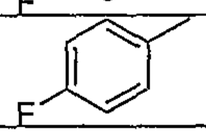
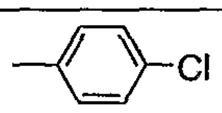
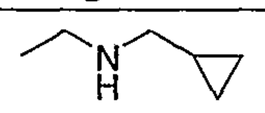
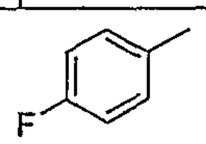
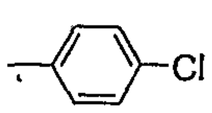
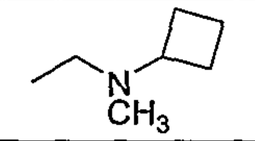
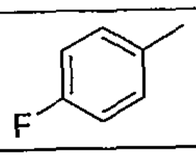
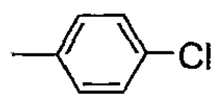
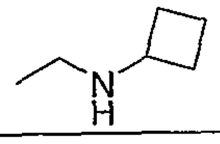
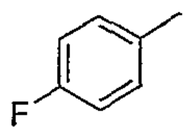
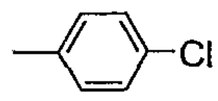
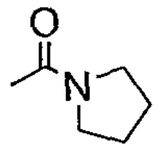
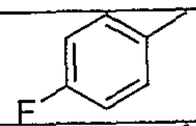
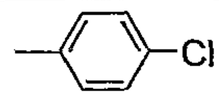
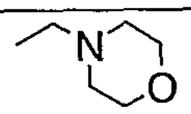
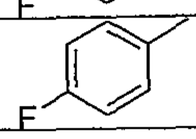
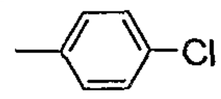
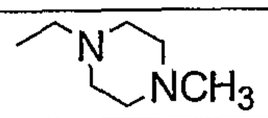
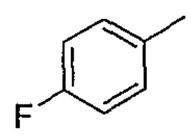
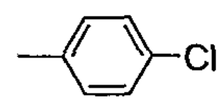
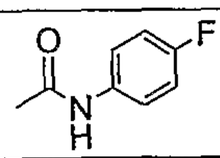
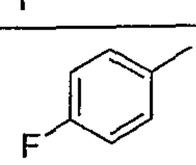
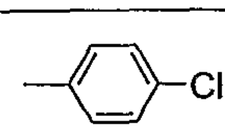
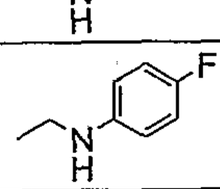
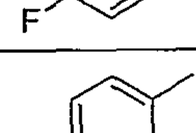
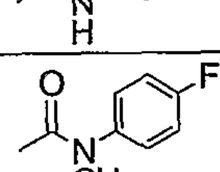
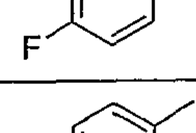
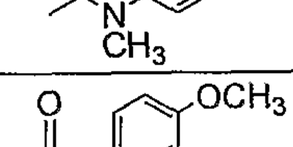
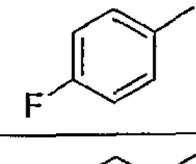
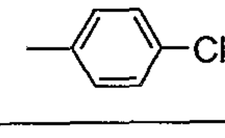
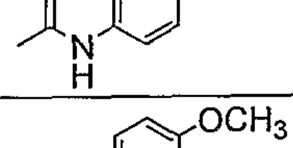
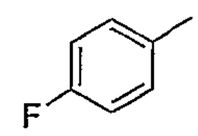
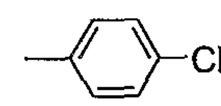
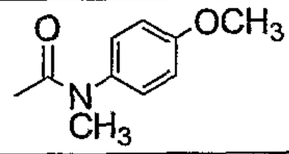
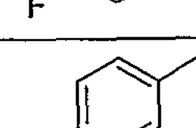
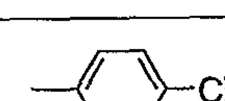
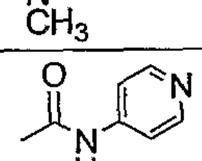
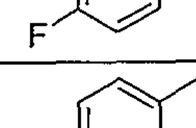
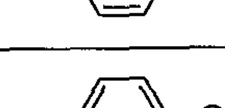
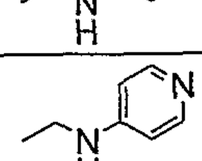
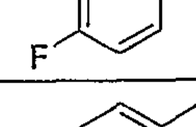
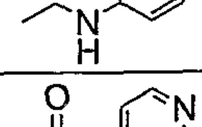
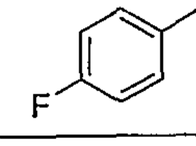
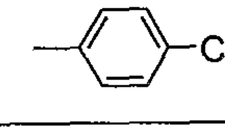
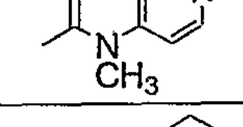
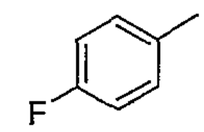
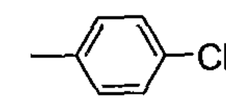
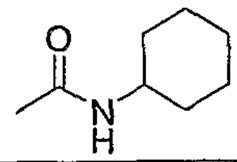
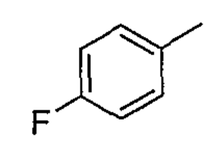
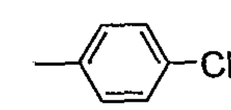
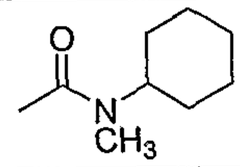
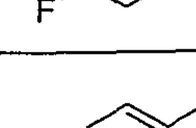
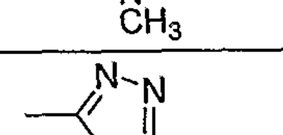
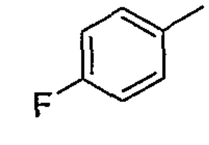
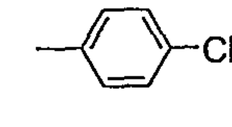
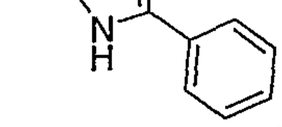
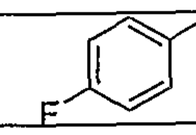
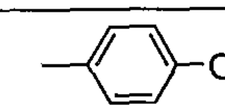
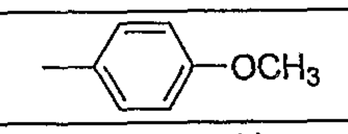
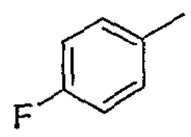
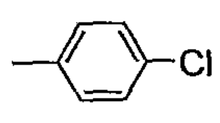
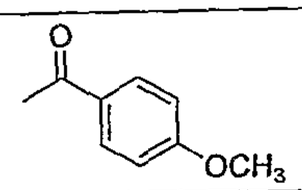
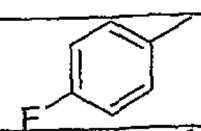
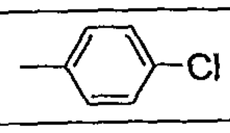
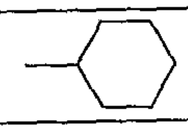
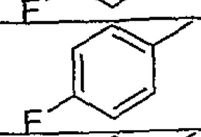
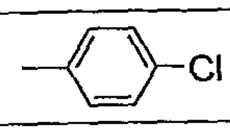
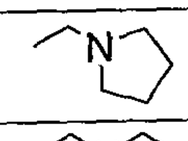
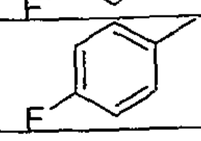
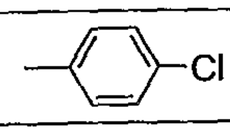
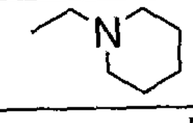
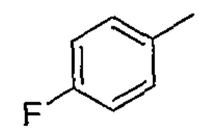
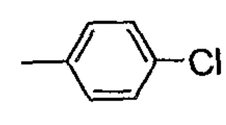
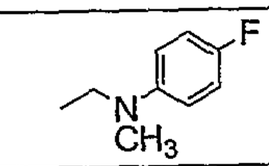
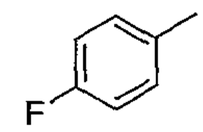
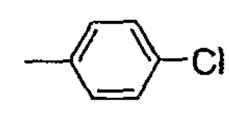
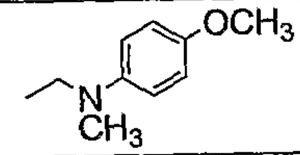
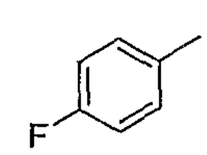
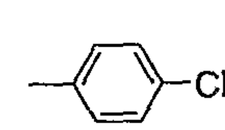
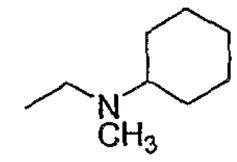
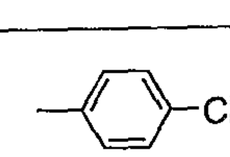
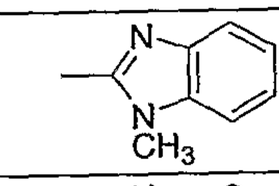
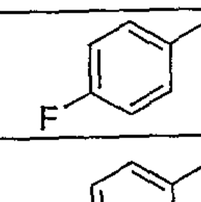
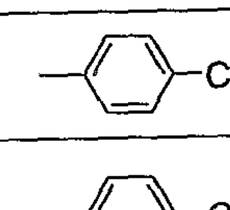
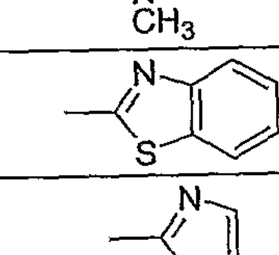
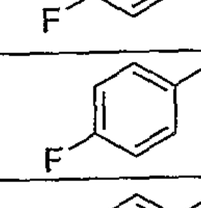
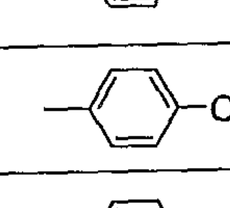
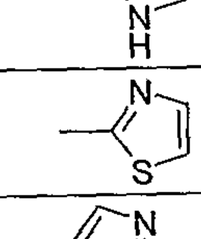
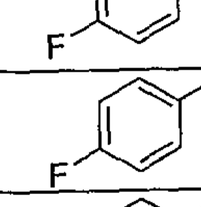
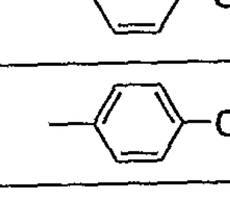
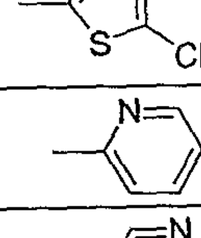
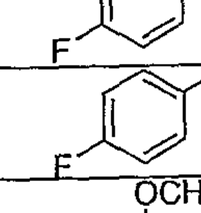
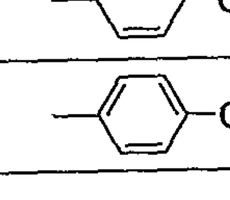
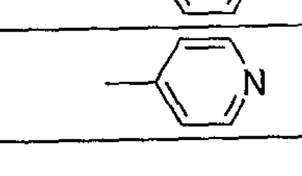
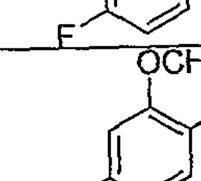
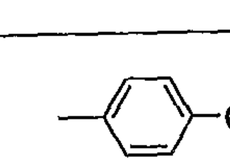
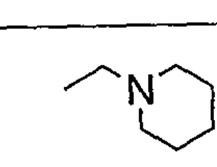
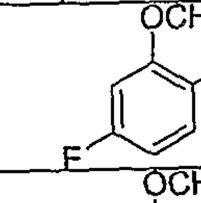
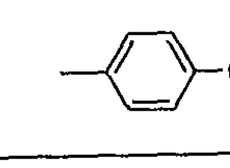
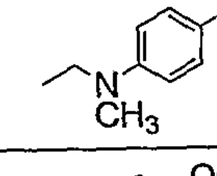
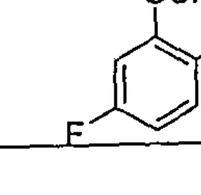
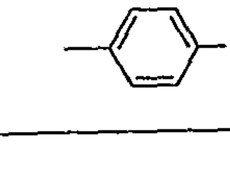
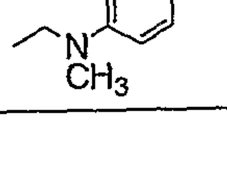
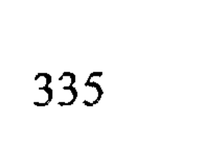
J-138			
J-139			
J-140			
J-141			
J-142			
J-143			
J-144			
J-145			

J-146			
J-147			
J-148			
J-149			
J-150			
J-151			
J-152			
J-153			
J-154			
J-155			
J-156			
J-157			
J-158			
J-159			
J-160			
J-161			

J-162			
J-163			
J-164			
J-165			
J-166			
J-167			
J-168			
J-169			
J-170			
J-171			
J-172			
J-173			
J-174			
J-175			
J-176			
J-177			
J-178			
J-179			
J-180			

J-181			
J-182			
J-183			
J-184			
J-185			
J-186			
J-187			
J-188			
J-189			
J-190			
J-191			
J-192			
J-193			
J-194			
J-195			
J-196			
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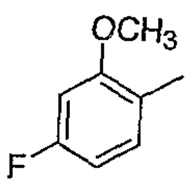
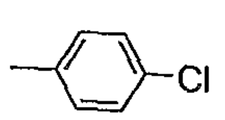
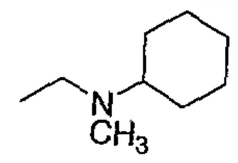
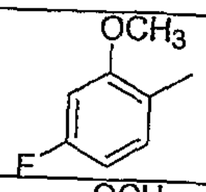
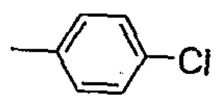
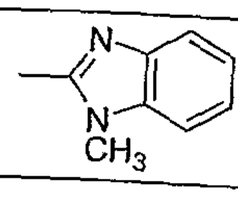
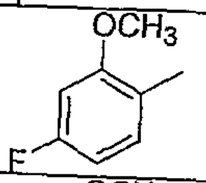
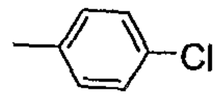
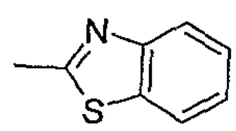
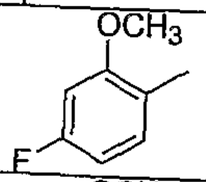
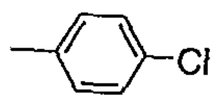
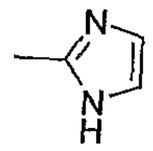
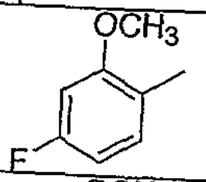
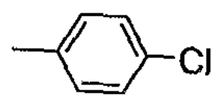
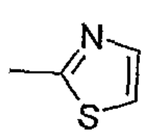
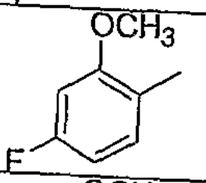
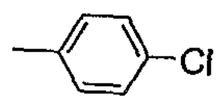
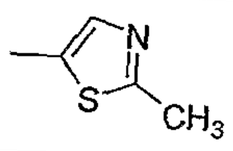
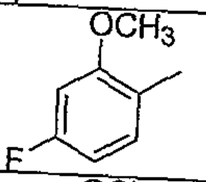
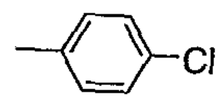
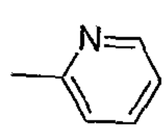
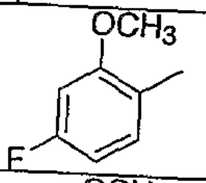
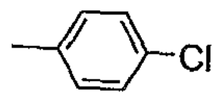
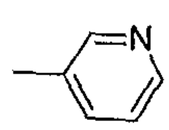
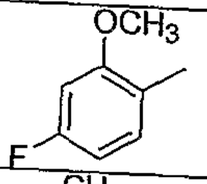
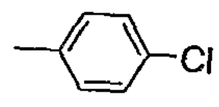
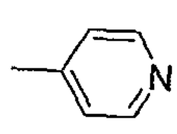
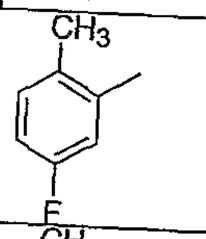
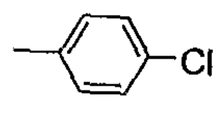
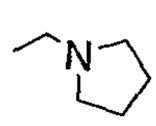
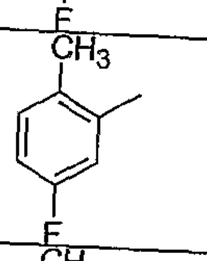
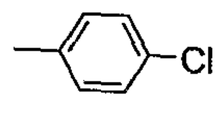
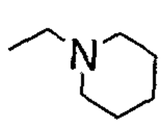
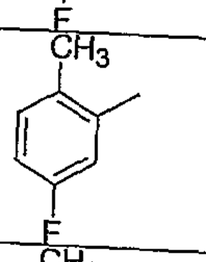
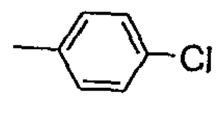
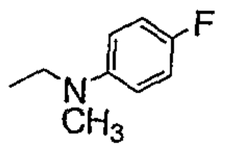
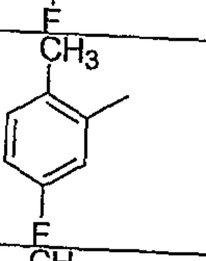
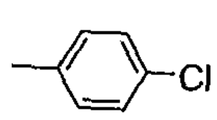
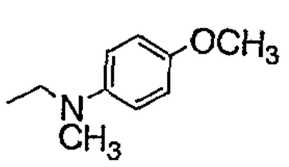
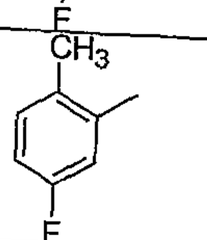
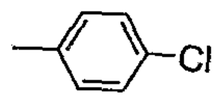
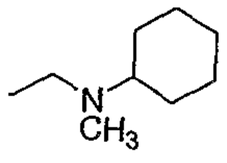
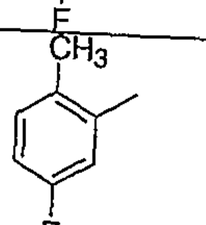
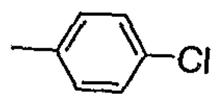
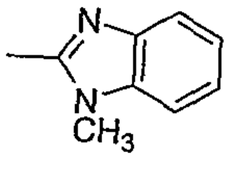
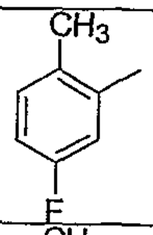
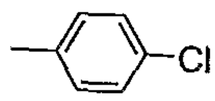
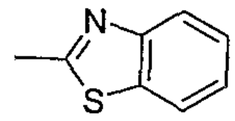
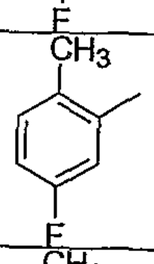
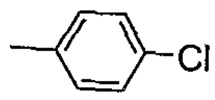
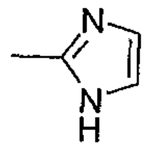
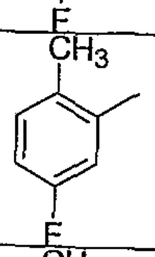
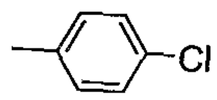
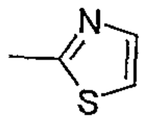
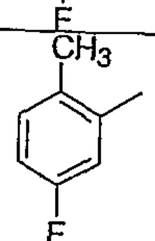
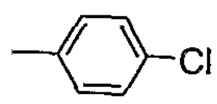
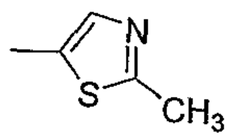
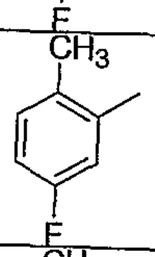
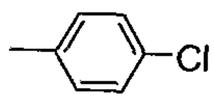
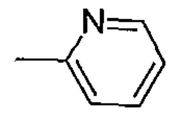
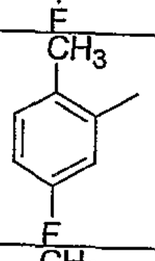
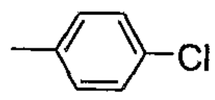
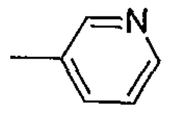
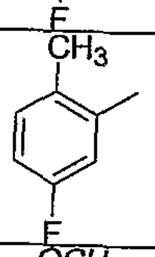
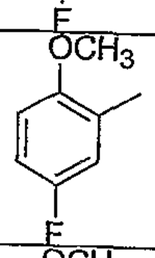
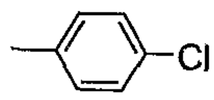
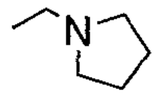
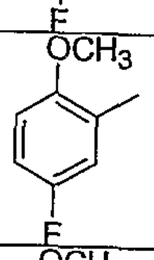
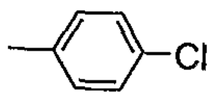
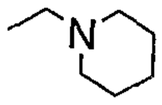
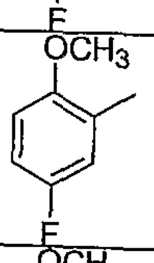
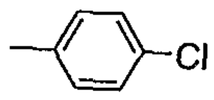
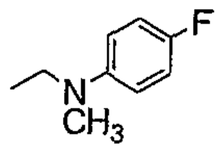
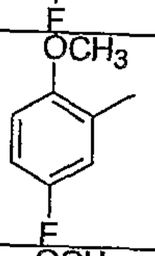
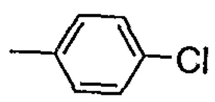
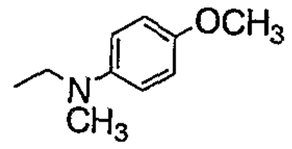
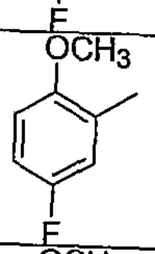
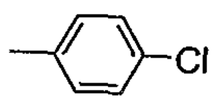
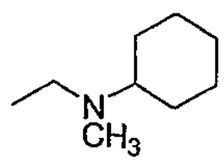
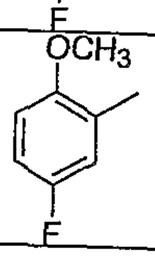
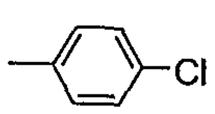
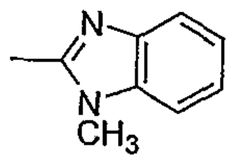
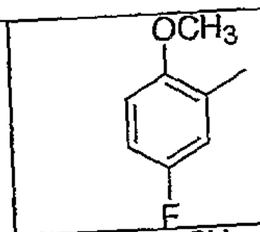
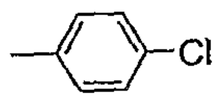
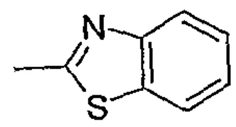
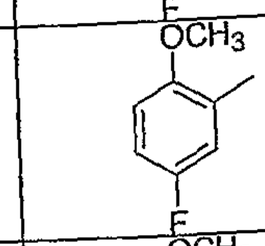
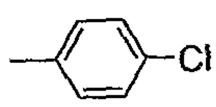
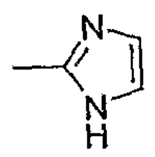
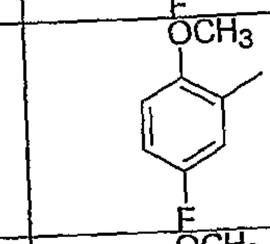
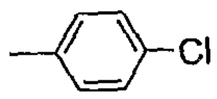
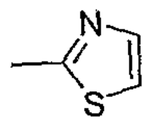
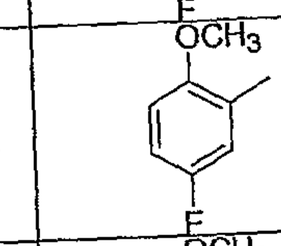
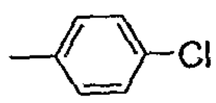
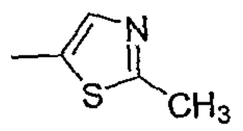
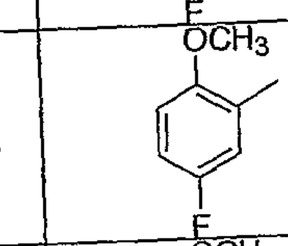
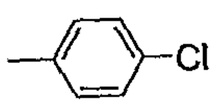
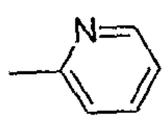
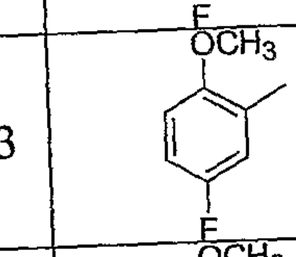
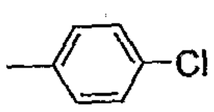
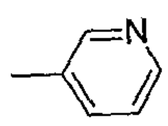
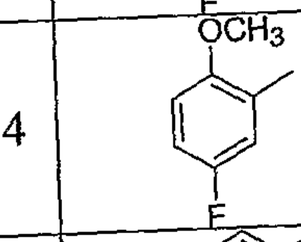
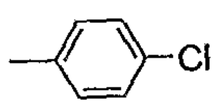
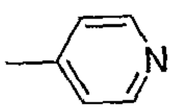
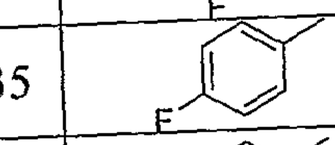
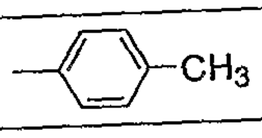
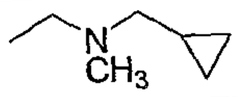
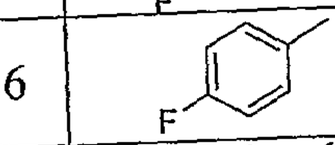
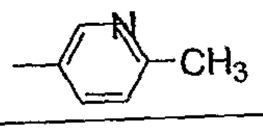
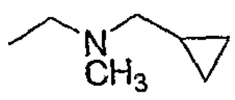
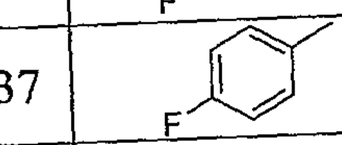
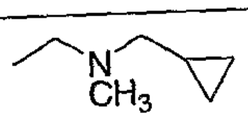
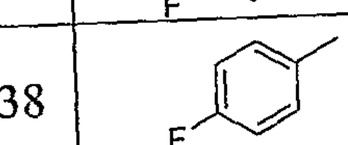
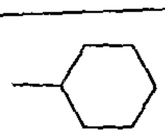
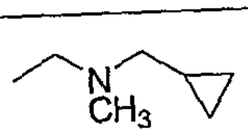
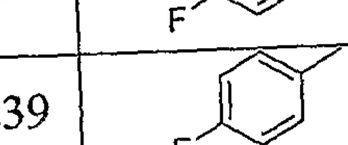
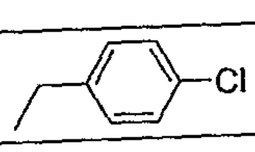
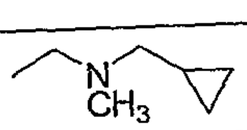
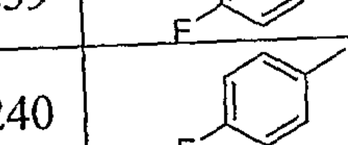
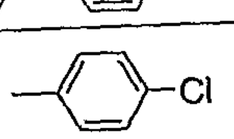
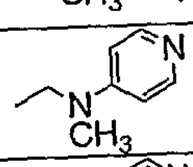
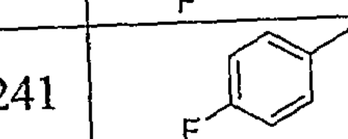
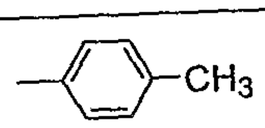
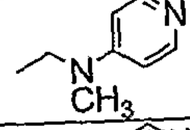
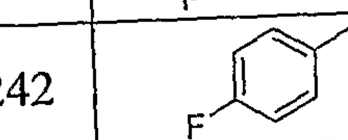
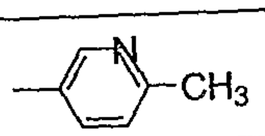
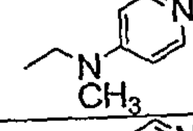
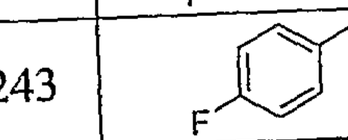
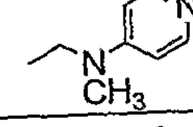
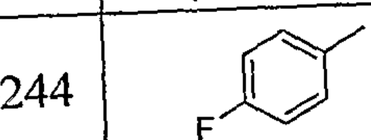
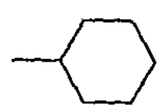
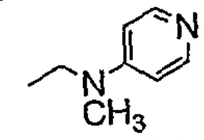
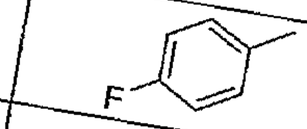
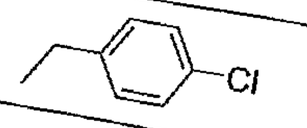
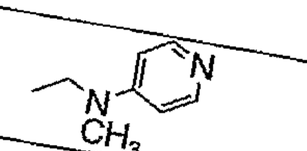
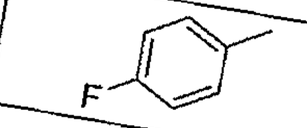
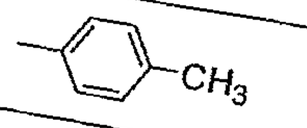
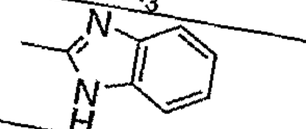
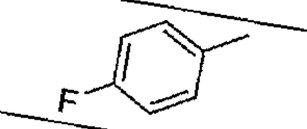
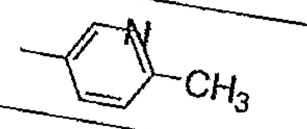
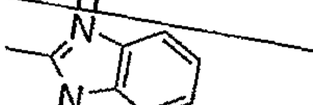
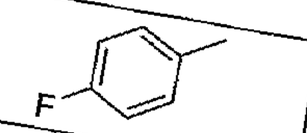
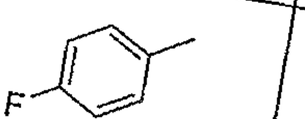
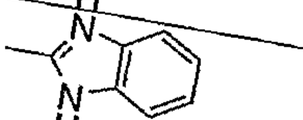
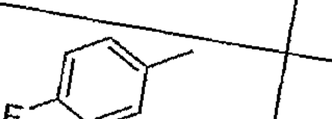
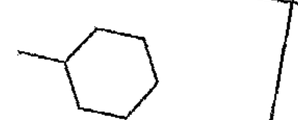
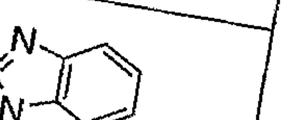
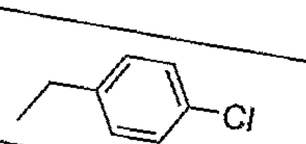
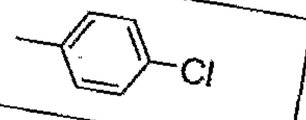
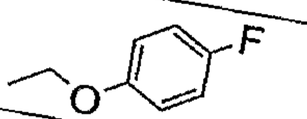
J-200			
J-201			
J-202			
J-203			
J-204			
J-205			
J-206			
J-207			
J-208			
J-209			
J-210			
J-211			
J-212			
J-213			
J-214			

J-215			
J-216			
J-217			
J-218			
J-219			
J-220			
J-221			
J-222			
J-223			
J-224			
J-225			
J-226			
J-227			

J-228			
J-229			
J-230			
J-231			
J-232			
J-233			
J-234			
J-235			
J-236			
J-237		CH_3	
J-238			
J-239			
J-240			
J-241			
J-242			
J-243		CH_3	
J-244			

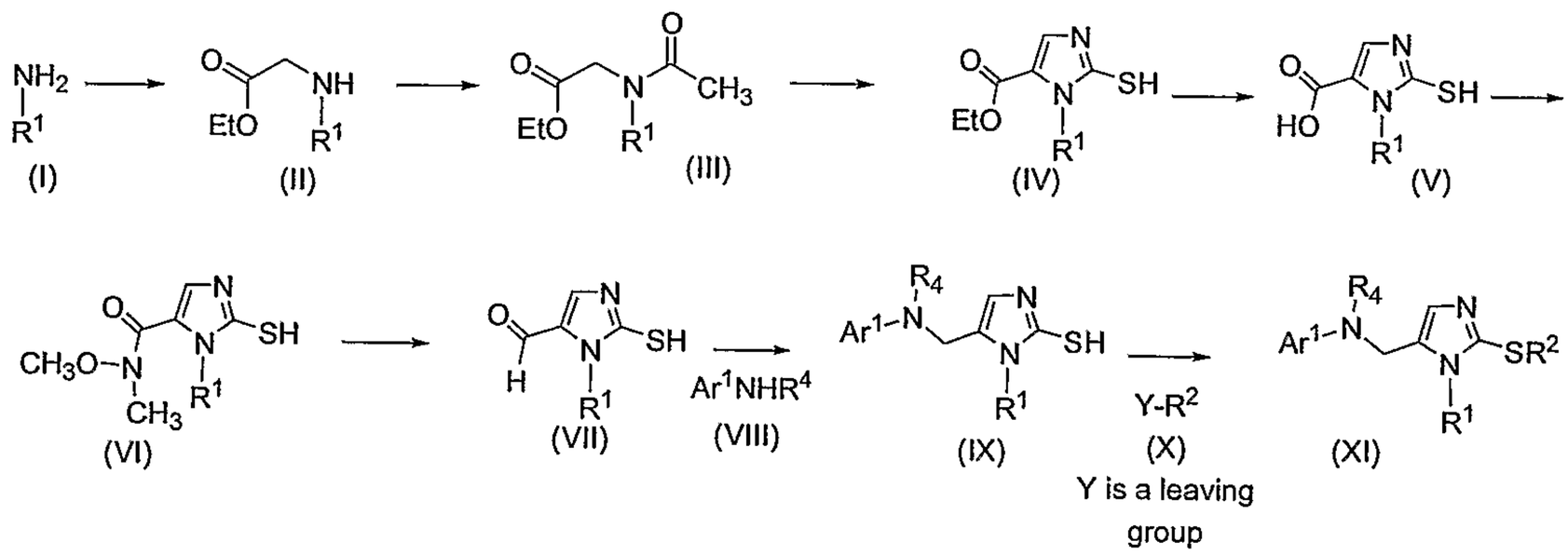
J-245			
J-246			
J-247			
J-248			
J-249		CH_3	
J-250			
J-251			
			

Ion channel-modulating compounds can be identified through both *in vitro* (e.g., cell and non-cell based) and *in vivo* methods. Representative examples of these methods are described in the Examples herein.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The compounds delineated herein can be synthesized using conventional methods, as illustrated in the schemes herein. In the schemes herein, unless expressly to the contrary, variables in chemical formulae are as defined in other formulae herein. For example, Ar^1, Ar^3, R^1, R^2, R^3 and R^4 in the schemes are defined as in any of the formulae herein, except where defined otherwise in the schemes.

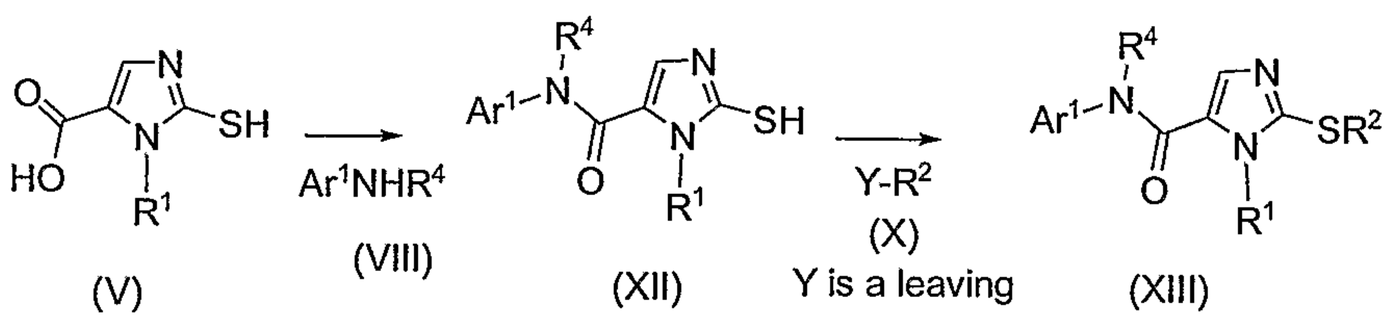
Scheme A1



Treatment of amine (I) under basic conditions (e.g., sodium acetate) with ethyl bromoacetate in solvent provides amino acid ester (II). Treatment of (II) in solvent with acetyl chloride provides (III). The imidazole (IV) is produced when (III) is treated with ethyl formate in solvent under basic conditions. Saponification of ester (IV) under basic conditions gives imidazole (V). Treatment of (V) with N, O-dimethylhydroxylamine under amide bond forming conditions (e.g., 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) in solvent gives amide (VI). Treatment of amide (VI) under reducing conditions (e.g., lithium aluminum hydride) in solvent provides aldehyde (VII). Treatment of (VII) with amine (VIII) under

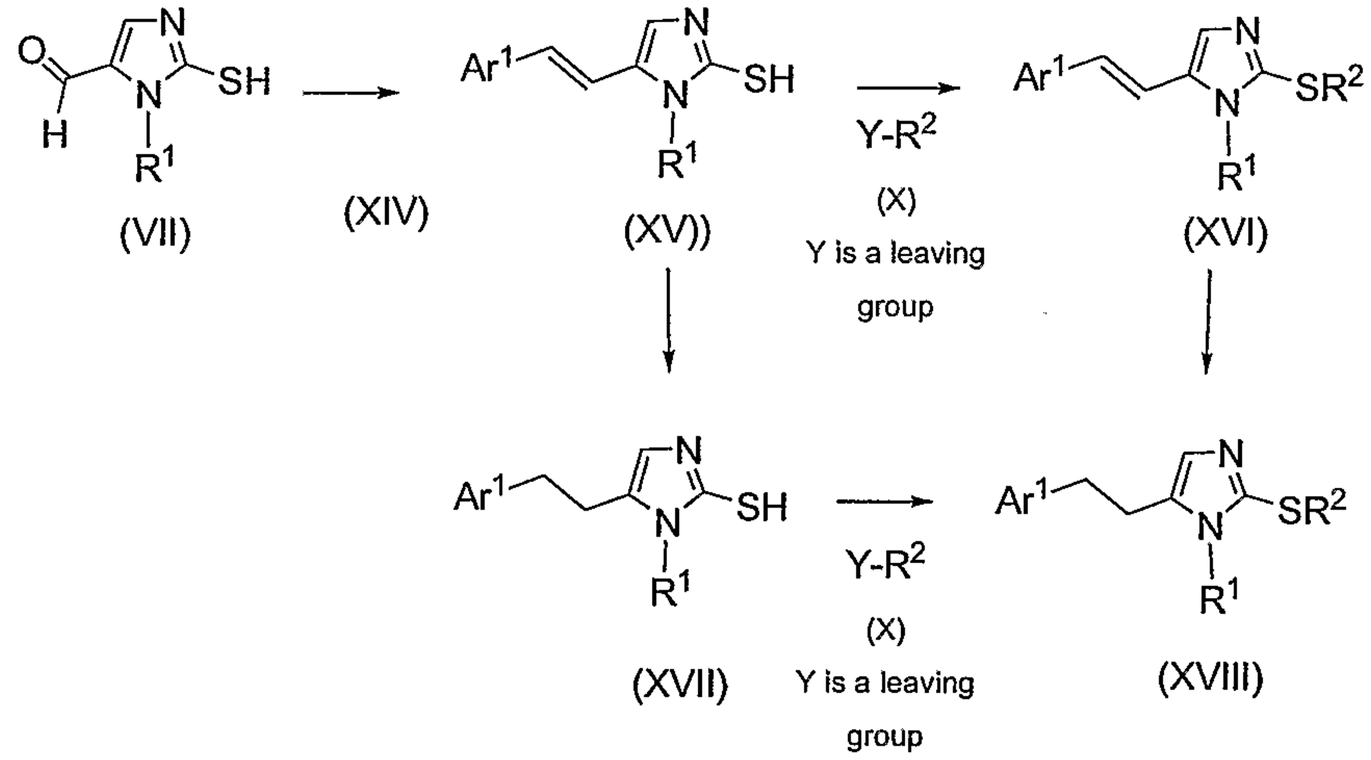
reducing conditions (e.g., lithium aluminum hydride, THF) provides (IX). Treatment of (IX) with (X) gives the desired compound (XI).

Scheme A2

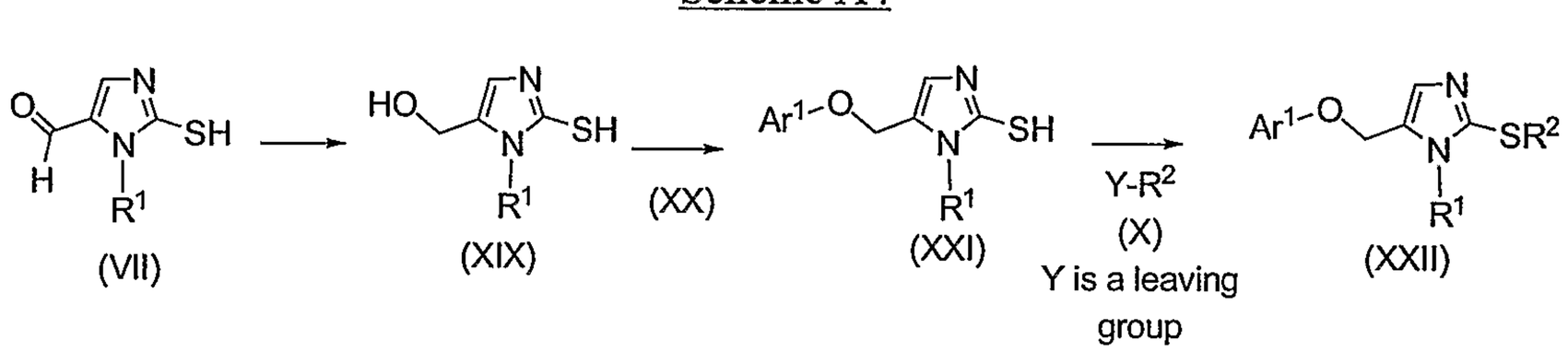


Treatment of carboxylic acid (V) with amine (VIII) under amide bond forming conditions (e.g., 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) in solvent gives amide (XII). Treatment of (XII) with (X) under basic conditions (e.g., K_2CO_3) in solvent provides (XIII).

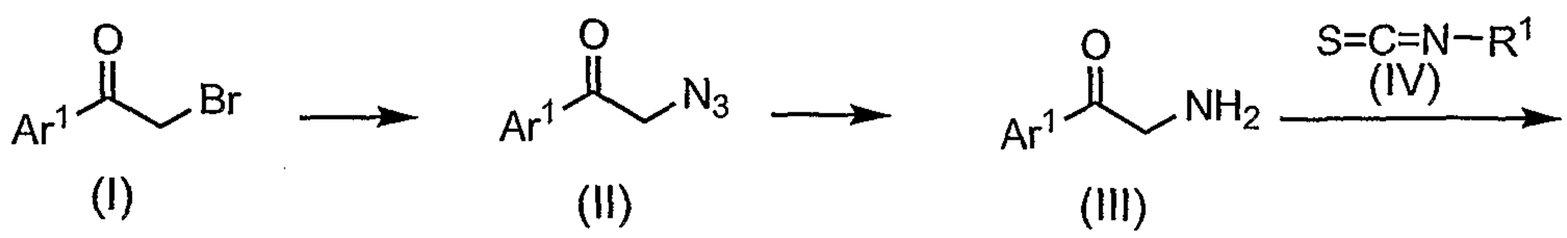
Scheme A3

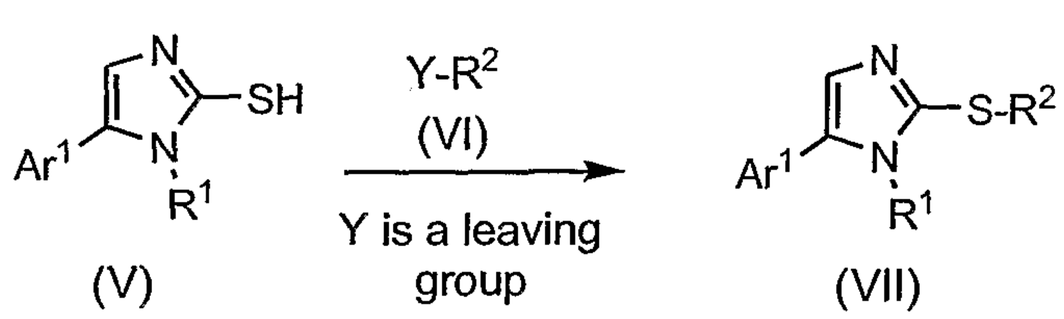


Scheme A4



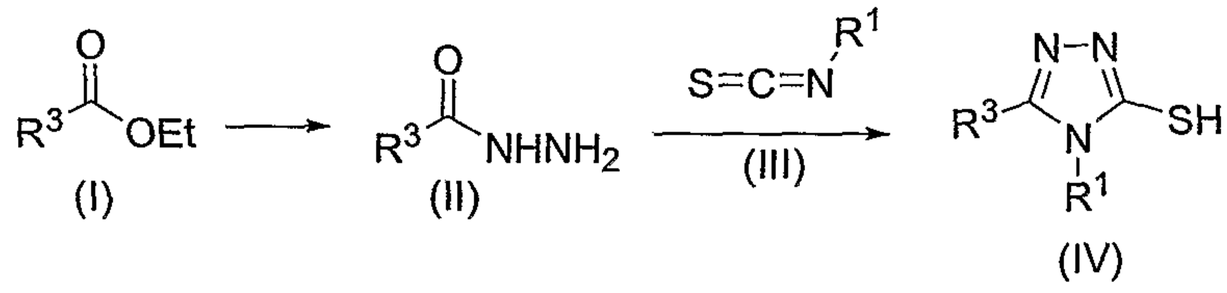
Scheme B1





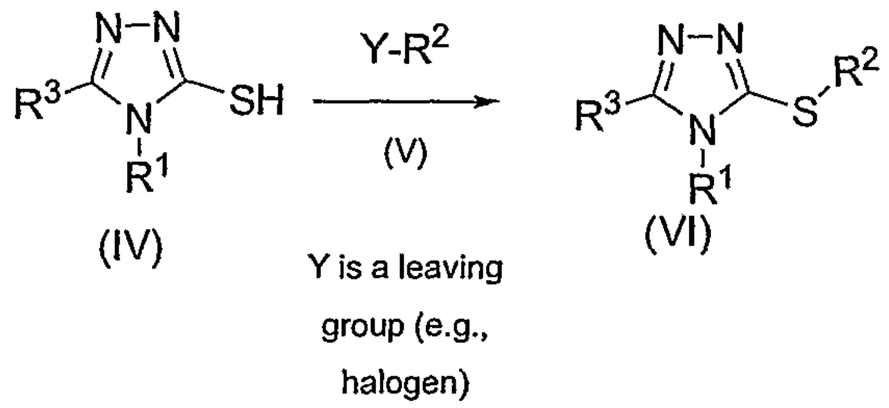
Treatment of the bromomethyl ketone (I) in solvent, such as DMSO, with sodium azide provides the azidomethyl ketone (II). Treatment of (II) with reducing conditions, such as palladium on carbon in aqueous HCl and H_2 atmosphere, provides the amine (III). The reaction of (III) and isothiocyanate (IV) under basic conditions, such as sodium hydrogencarbonate, in a solvent, such as ethanol, provides thioimidazole (V). The reaction of (V) and (VI) under basic condition, such as potassium carbonate, provides imidazole (VII).

Scheme C1



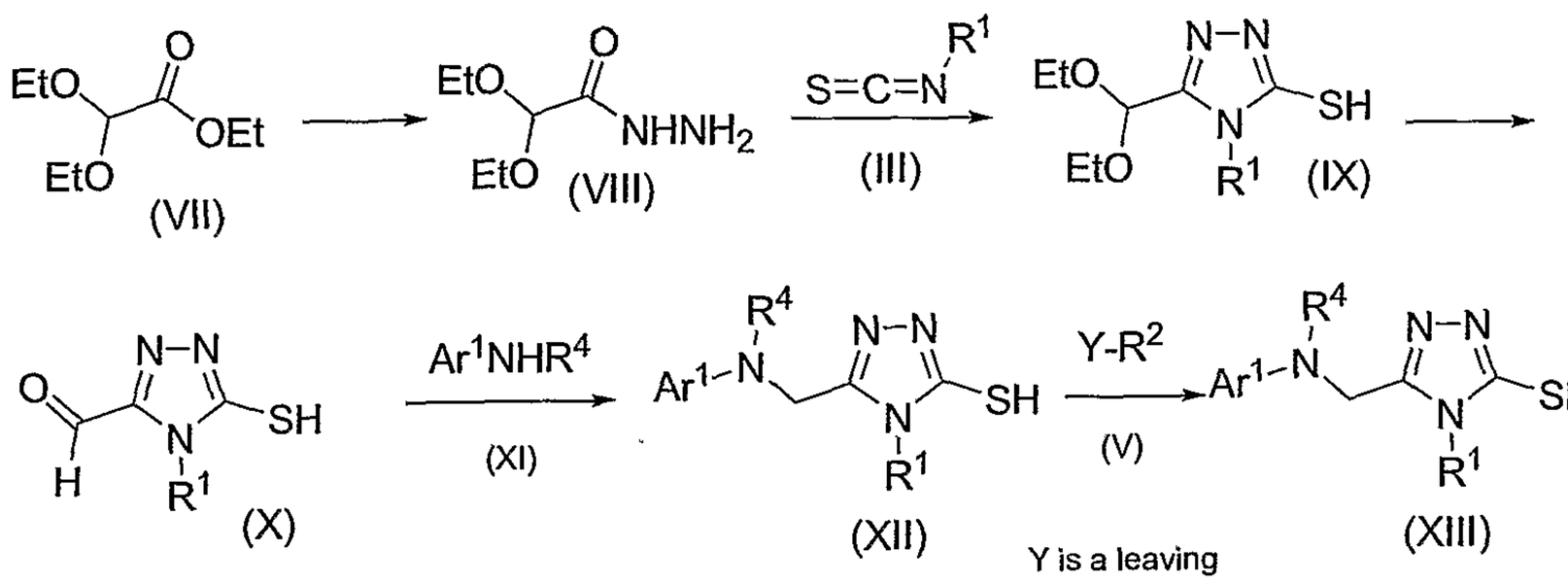
Treatment of ethyl ester (I) with hydrazine in solvent (e.g., ethanol) provides hydrazide (II). Treatment of (II) with thioisocyanate (III) under aqueous basic conditions gives triazole thiol (IV).

Scheme C2



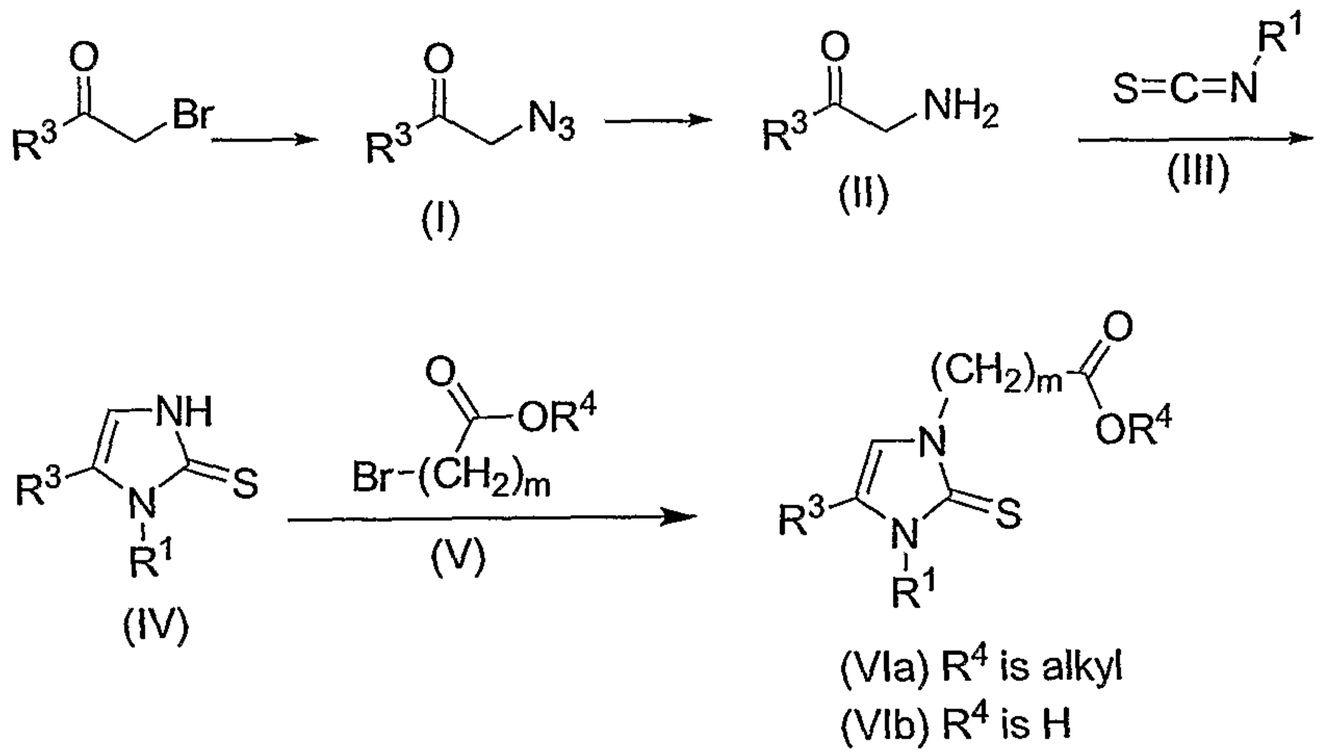
Treatment of (IV) with (V) under basic conditions (e.g., K_2CO_3 in acetone) gives (VI).

Scheme C3



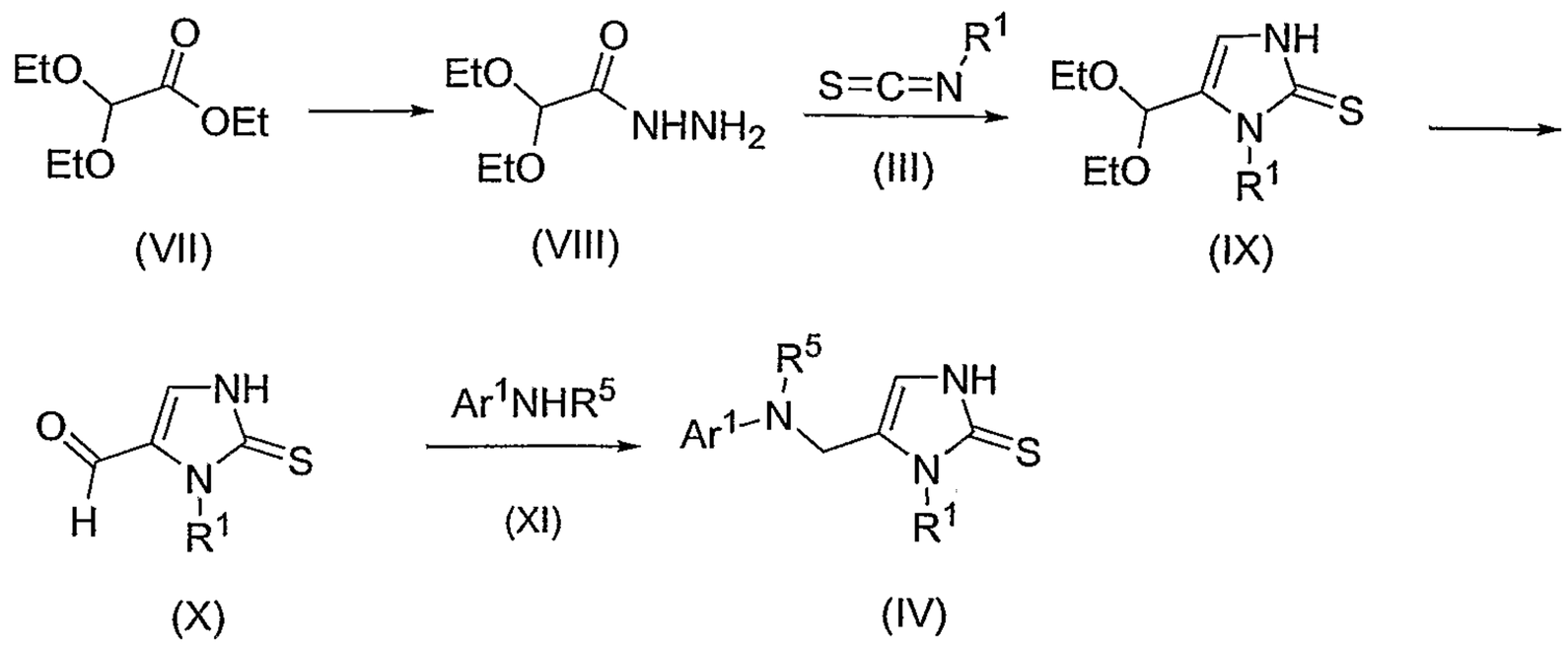
Treatment of ethyl diethoxy acetate (VII) with hydrazine in solvent (e.g., ethanol) provides hydrazide (VIII). Treatment of (VIII) with thioisocyanate (III) aqueous basic conditions gives triazole (IX) which turn provides aldehyde (X) upon treatment with aqueous acidic conditions. Treatment of (X) with (V) under basic conditions (e.g., K_2CO_3 in acetone) provides (XIII).

Scheme D-1



Treatment of the bromomethyl compound with sodium azide provides azidomethyl compound (I). Treatment of (I) under reducing conditions, such as palladium on carbon in aqueous HCl and H_2 atmosphere, provides amine (II). Treatment of (II) with isothiocyanate (III) provides imidazole (IV). N-Alkylated imidazole (V1a) is produced from the reaction of (IV) with 3-bromo-proprionate or 4-bromo-butyrate (V). Saponification of the ester (VIa) gives the carboxylic acid (VIb).

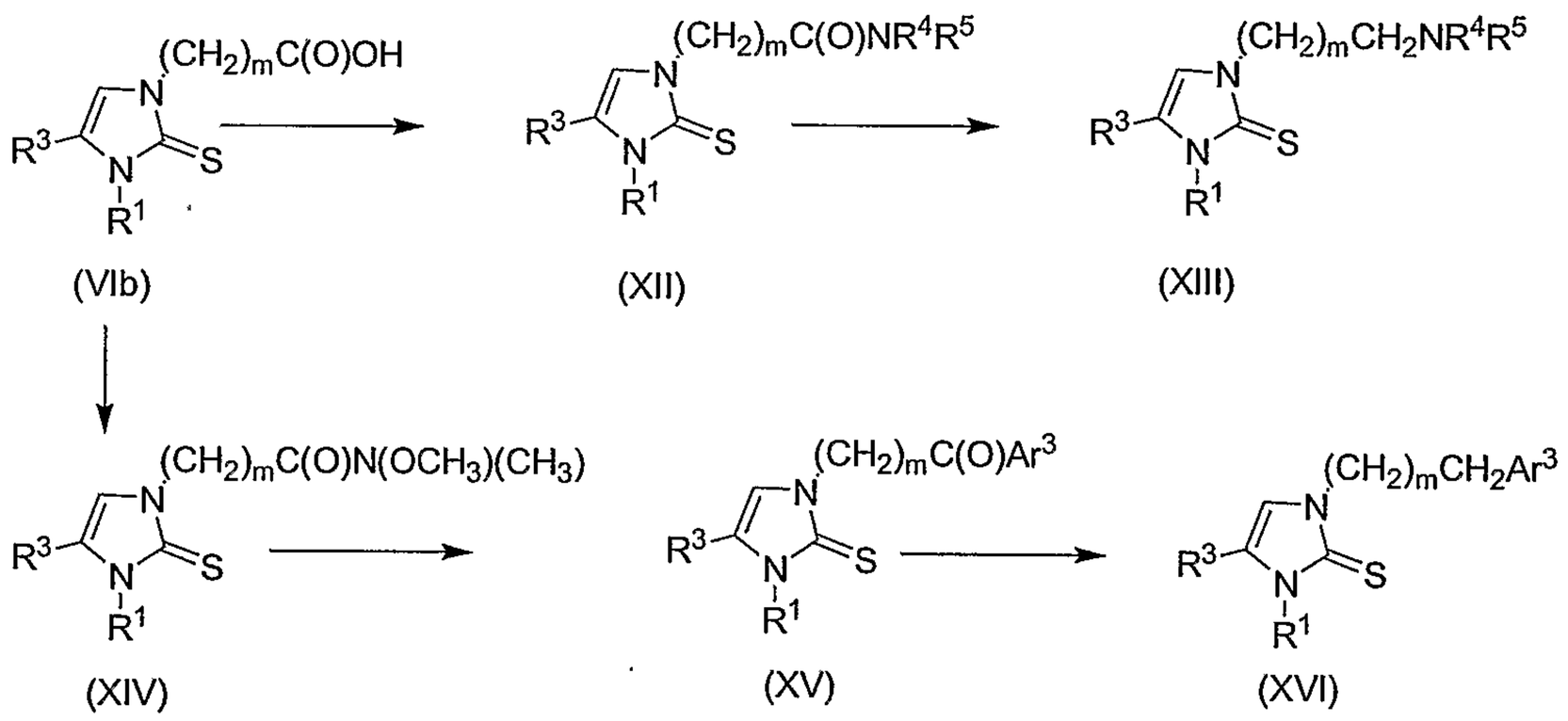
Scheme D-2



Alternatively, imidazole (IV) is prepared by the following sequence.

Treatment of ethyl diethoxy acetate (VII) with hydrazine in solvent (e.g., ethanol) provides hydrazide (VIII). Treatment of (VIII) with thioisocyanate (III) under aqueous basic conditions gives imidazole (IX) which in turn provides aldehyde (X) under aqueous acidic conditions. Reductive amination of (X) and amine (XI) provides (IV).

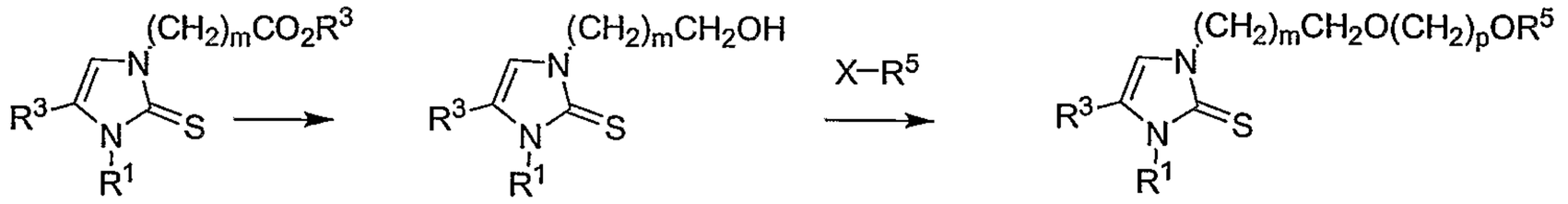
Scheme D-3



The reaction of carboxylic acid (VIb) with the appropriately substituted amine under standard coupling procedures provides the desired amide (XII). Reduction of the amide under common reducing conditions (e.g., diborane or lithium aluminum hydride) provides the corresponding amine (XIII). Alternatively, treatment of (VIb) with Weinreb's reagent provides the amide (XIV). Treatment of the amide (XIV) under standard conditions with an organometallic reagent (e.g., aryl lithium or aryl

magnesium halide) provides the ketone (XV). Reduction of the ketone under a variety conditions affords the desired product (XVI).

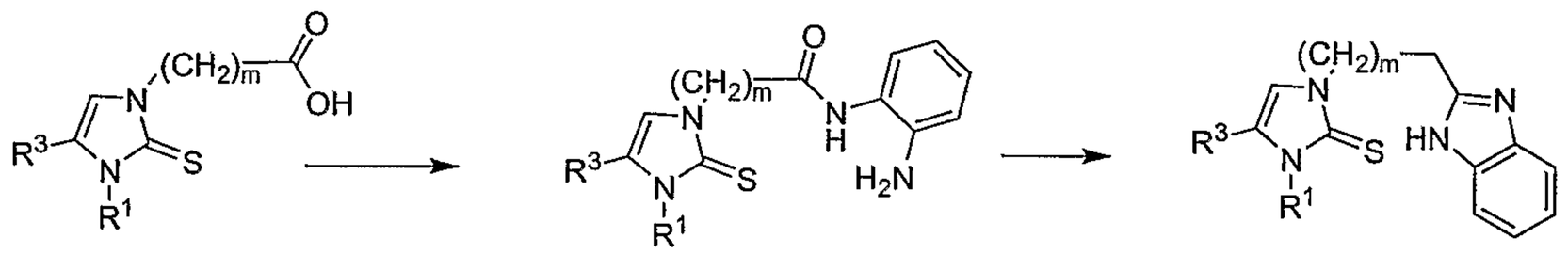
Scheme D-4



(VIa) (XVII) (XVIII)

Treatment of ester (VIa) under standard reducing conditions (e.g., lithium aluminum hydride) gives alcohol (XVII). Treatment of (XVII) under standard ether forming conditions (e.g., NaH, benzylbromide) gives (XVIII).

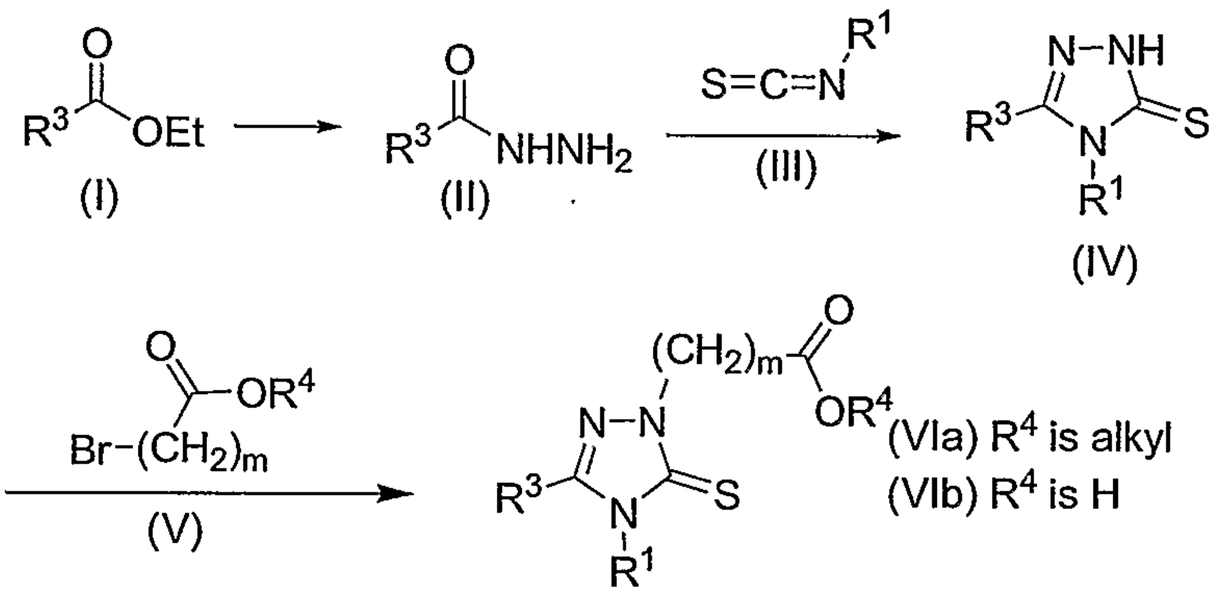
Scheme D-5



(VIb) (XIX) (XX)

An alternative route to obtain heteroaryl derivatives is to react the activated acid of (VIb) with the appropriate substrate followed by cyclization to provide the desired product. For example as depicted in Scheme D-5, reaction of the activated acid of (VIb) with benzene-1,2-diamine provides the intermediate amide (XIX), which is cyclized to afford the benzimidazole derivative (XX).

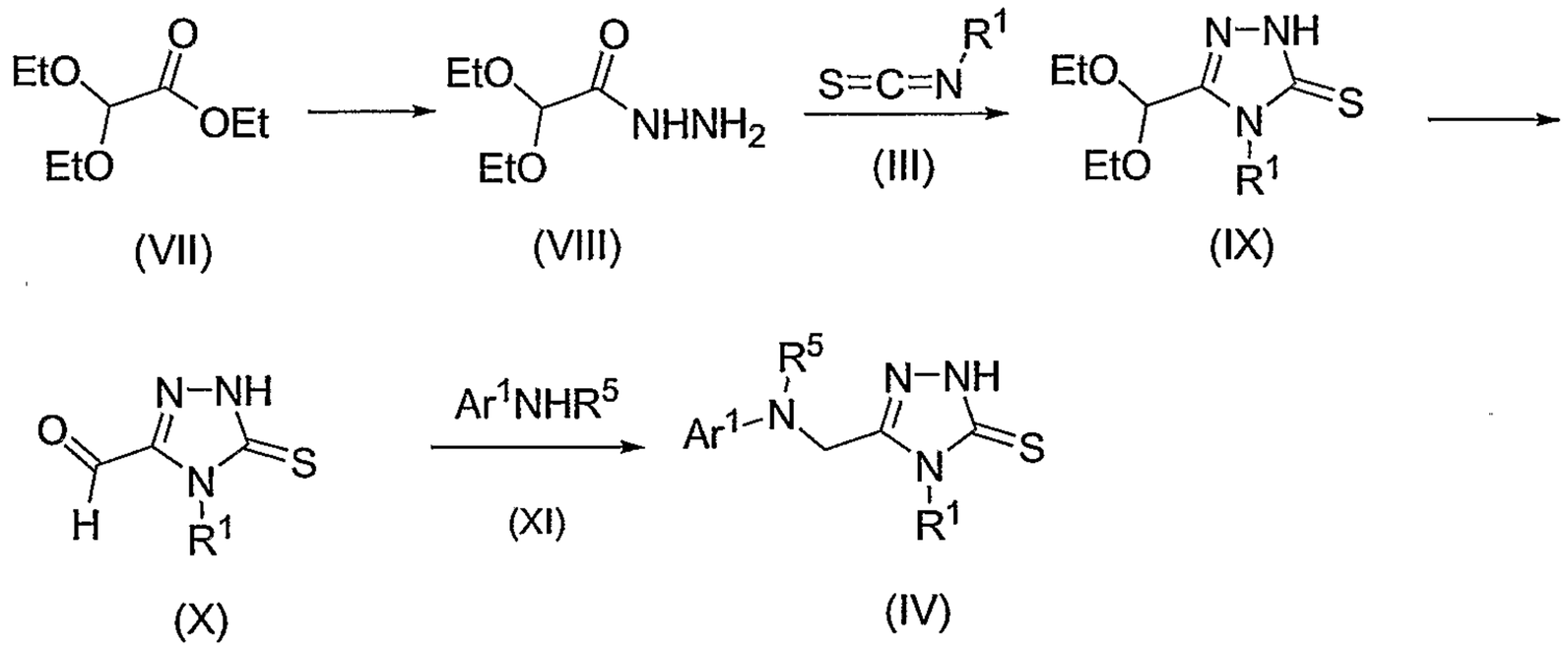
Scheme E-1



Treatment of ethyl ester (I) with hydrazine in solvent (e.g., ethanol) provides hydrazide (II). Treatment of (II) with thioisocyanate (III) under aqueous basic

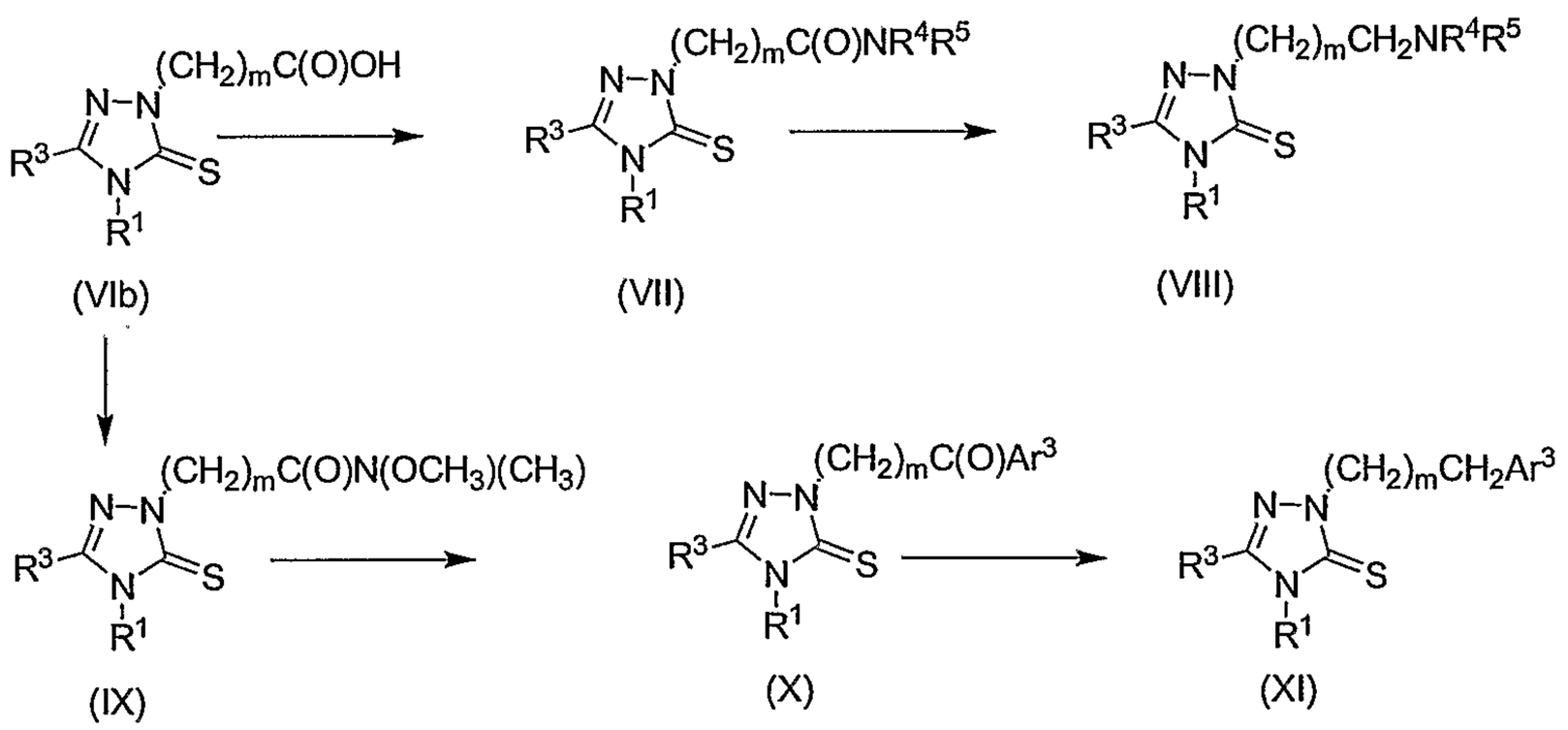
conditions gives triazole thione (IV). N-Alkylated triazole (V1a) is produced from the reaction of (IV) with 3-bromo-proprionate or 4-bromo-butyrate (V). Saponification of the ester (VIa) gives the carboxylic acid (VIb).

Scheme E-2



Alternatively, triazole (IV) is prepared by the following sequence. Treatment of ethyl diethoxy acetate (VII) with hydrazine in solvent (e.g., ethanol) provides hydrazide (VIII). Treatment of (VIII) with thioisocyanate (III) under aqueous basic conditions gives triazole (IX) which in turn provides aldehyde (X) under aqueous acidic conditions. Reductive amination of (X) and amine (XI) provides (IV).

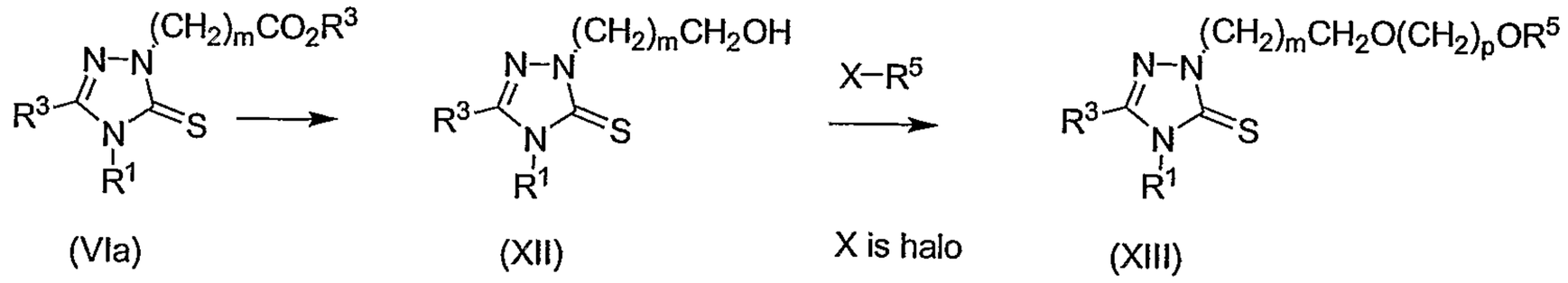
Scheme E-3



The reaction of carboxylic acid (VIb) with the appropriately substituted amine under standard coupling procedures provides the desired amide (VII). Reduction of the amide under common reducing conditions (e.g., diborane or lithium aluminum hydride) provides the corresponding amine (VIII). Alternatively, treatment of (VIb) with Weinreb's reagent provides the amide (IX). Treatment of the amide (IX) under

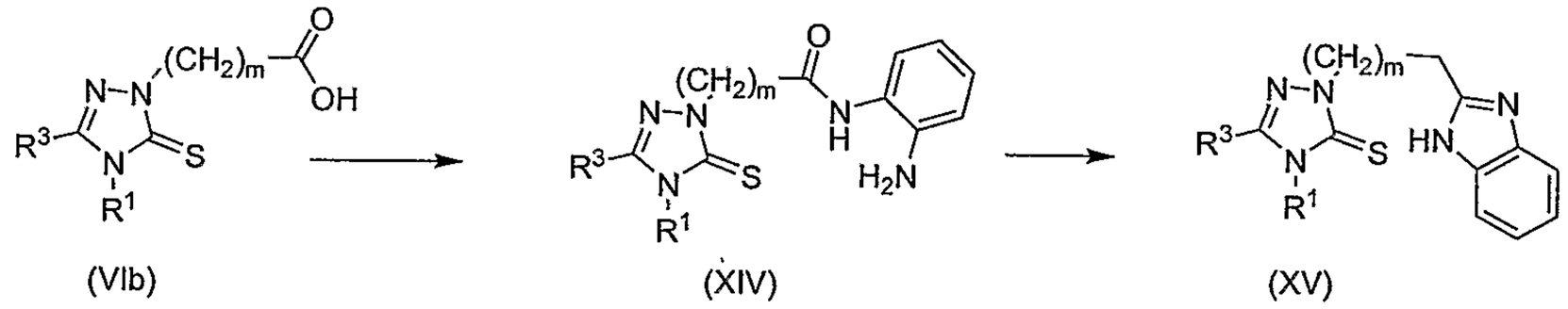
standard conditions with an organometallic reagent (e.g., aryl lithium or aryl magnesium halide) provides the ketone (X). Reduction of the ketone under a variety conditions affords the desired product (XI).

Scheme E-4



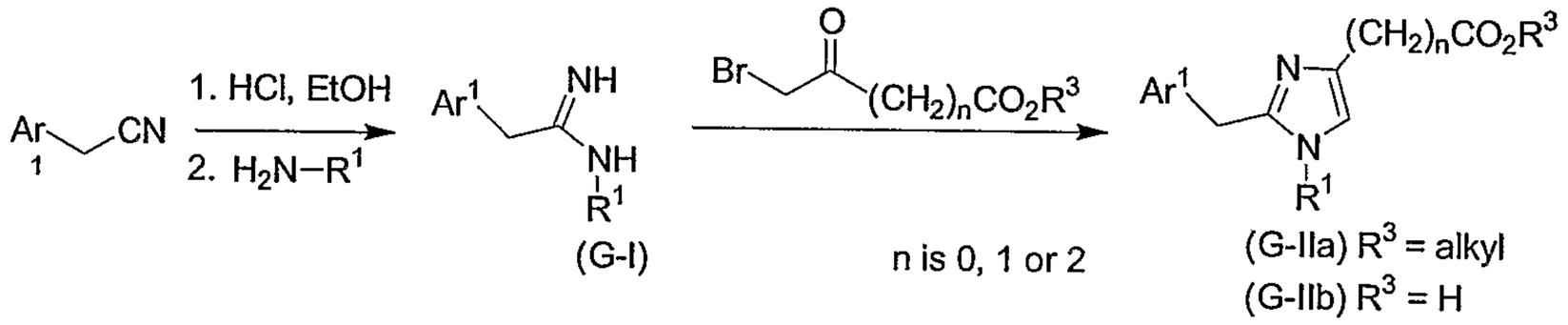
Treatment of ester (VIa) under standard reducing conditions (e.g., lithium aluminum hydride) gives alcohol (XII). Treatment of (XII) under standard ether forming conditions (e.g., NaH, benzylbromide) gives (XIII).

Scheme E-5



An alternative route to obtain heteroaryl derivatives is to react the activated acid of (VIb) with the appropriate substrate followed by cyclization to provide the desired product. For example as depicted in Scheme E-5, reaction of the activated acid of (VIb) with benzene-1,2-diamine provides the intermediate amide (XIV), which is cyclized to afford the benzimidazole derivative (XV).

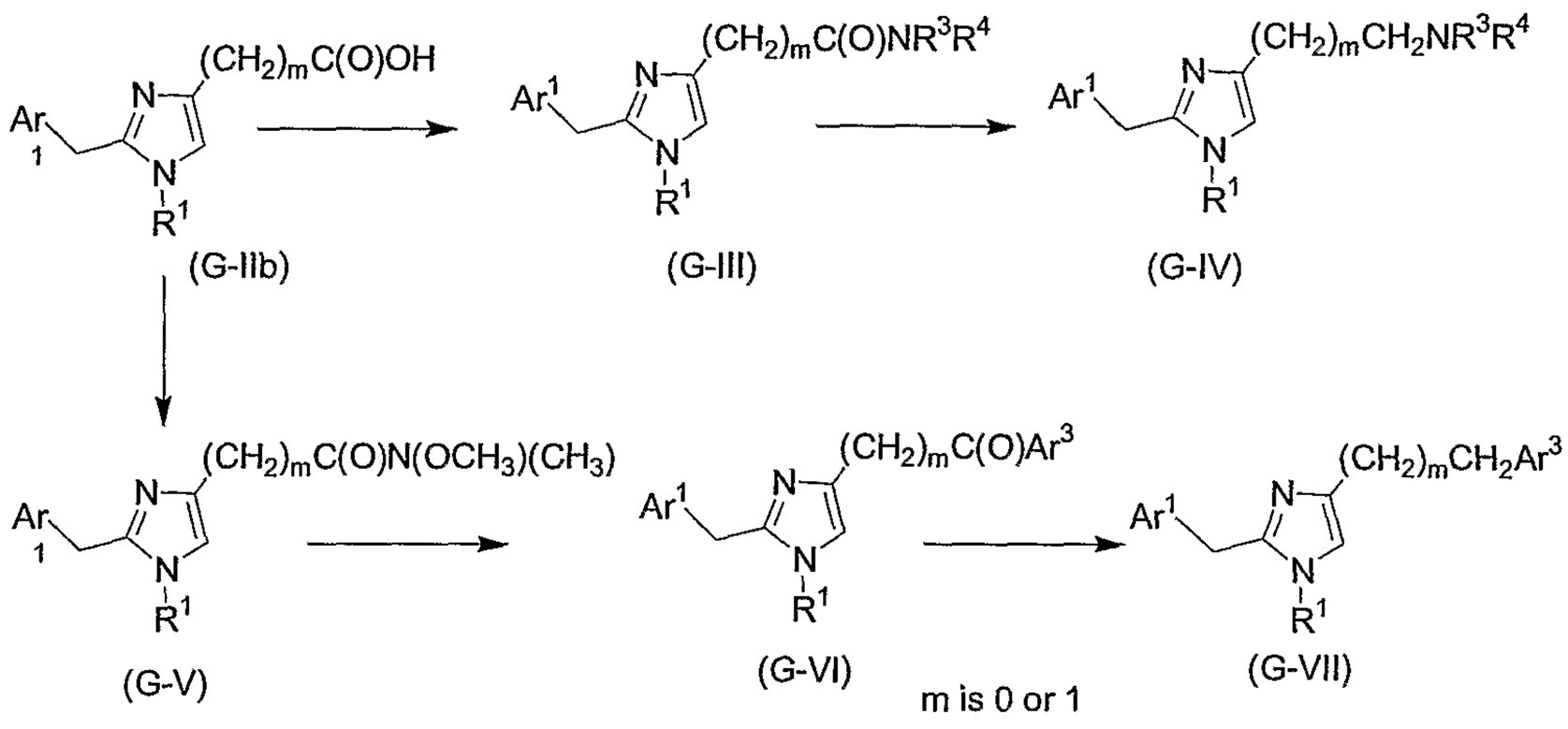
Scheme G-1



Treatment of an aryl nitrile with an alcohol under acidic conditions provides the alkoxy imidate intermediate, which is treated with the appropriate substituted

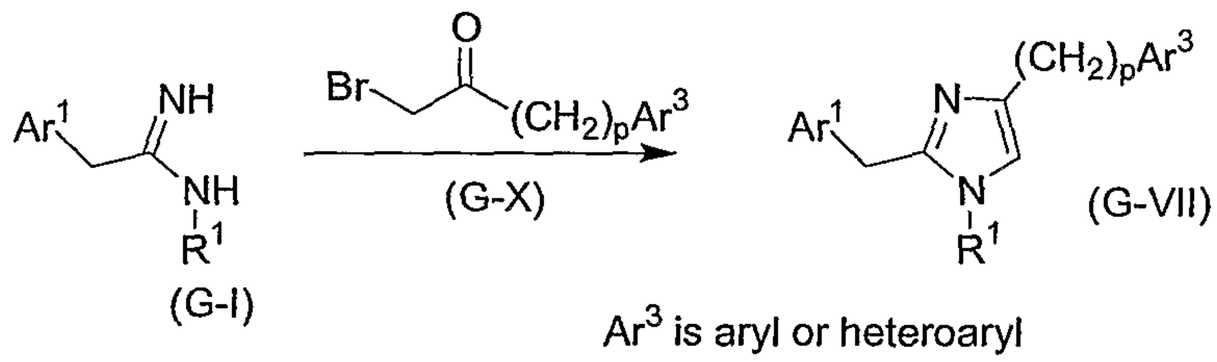
amine under catalytic conditions (e.g., ethanolic HCl; CuCl; Ln(III) ions) to provide the substituted amidine (G-I). Treatment of amidine (G-I) with a bromopyruvate or a 4-bromo-3-oxo-butyrate or a 5-bromo-oxo-pentanoate under basic conditions provides the imdiazole ester (G-IIa), which is hydrolyzed to provide the corresponding acid derivative (G-IIb).

Scheme G-2



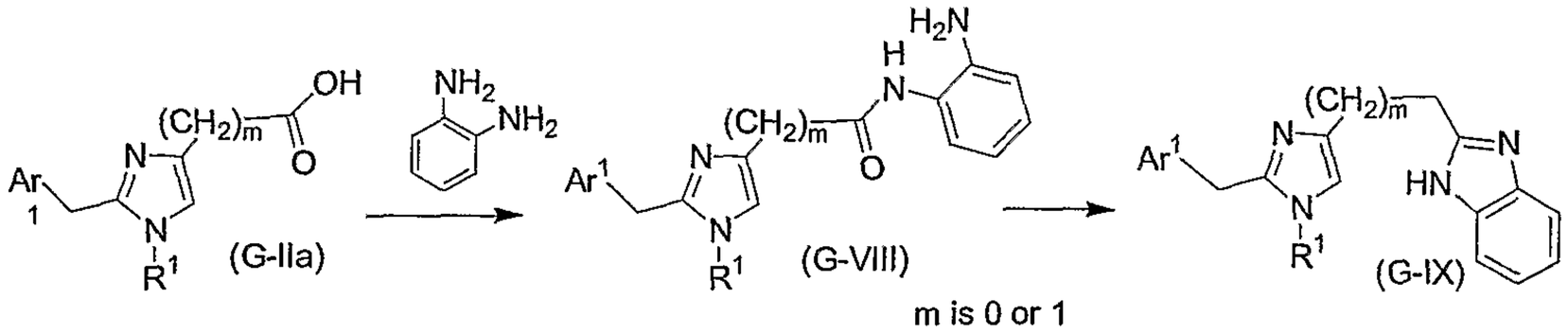
Reaction of the acid (G-IIb) with the appropriately substituted amine under standard coupling procedures provides the desired amide (G-III). Reduction of the amide with common reducing agents such as diborane or lithium aluminum hydride provides the corresponding amine (G-IV). Alternatively treatment of the acid (G-IIb) with Weinreb's reagent provides amide (G-V). Treatment of the amide under standard condition with an organometallic reagent (ex. aryl lithium or aryl magnesium halide) provides the ketone (G-VI). Reduction of the ketone under a variety of conditions affords the desired product (G-VII).

Scheme G-3



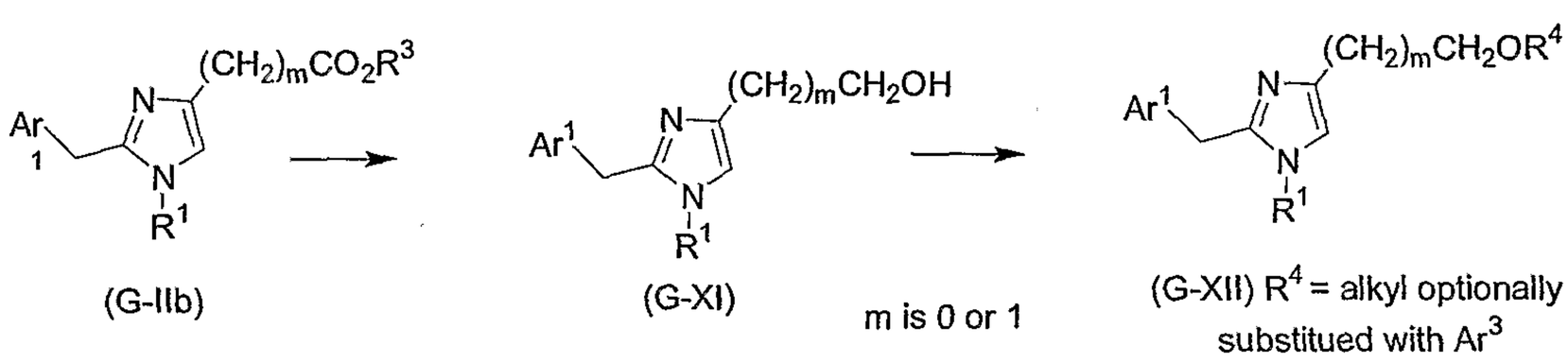
Alternatively treatment of amidine (G-I) with (G-X) provides the desired imidazole (G-VII).

Scheme G-4



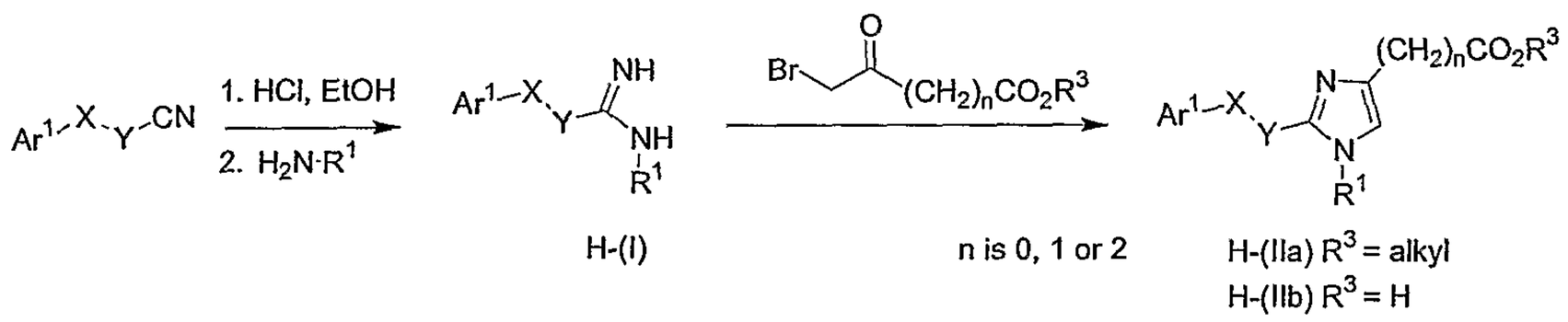
An alternative route to obtain heteroaryl derivatives is to react the activated acid of (G-IIb) with the appropriate substrate followed by cyclization to provide the desired product. For example as depicted in Scheme G-4, reaction of the activated acid of (G-IIb) with benzene-1,2-diamine provides the intermediate amide (G-VIII), which is cyclized to afford the benzimidazole derivative (G-IX).

Scheme G-5



Treatment of carboxylic acid (G-IIb) under standard reducing conditions (e.g., lithium aluminum hydride) gives (G-XI). Treatment of (G-XI) under standard ether forming conditions (e.g., NaH, halo-R^4) gives (G-XII).

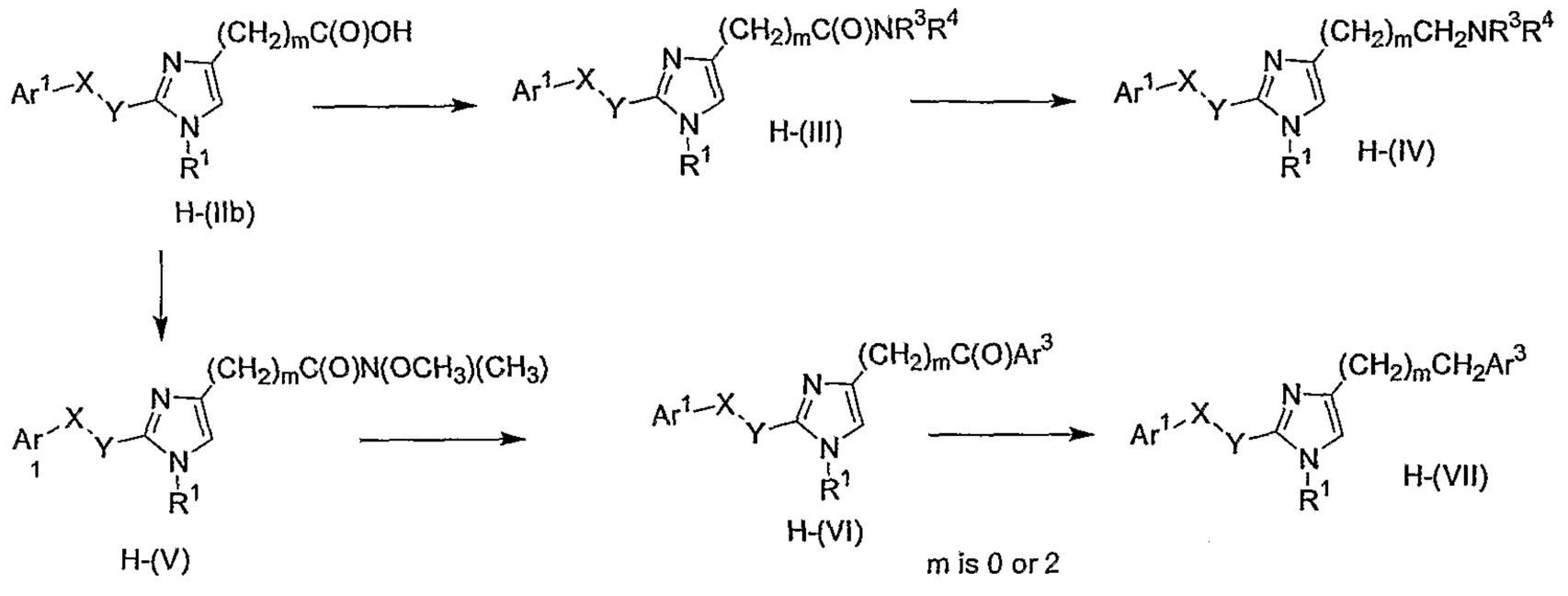
Scheme H-1



Treatment of an aryl nitrile with an alcohol under acidic conditions provides the alkoxy imidate intermediate, which is treated with the appropriate substituted amine under catalytic conditions (e.g., ethanolic HCl; CuCl; Ln(III) ions) to provide the substituted amidine H- (I). Treatment of amidine H- (I) with a bromopyruvate or

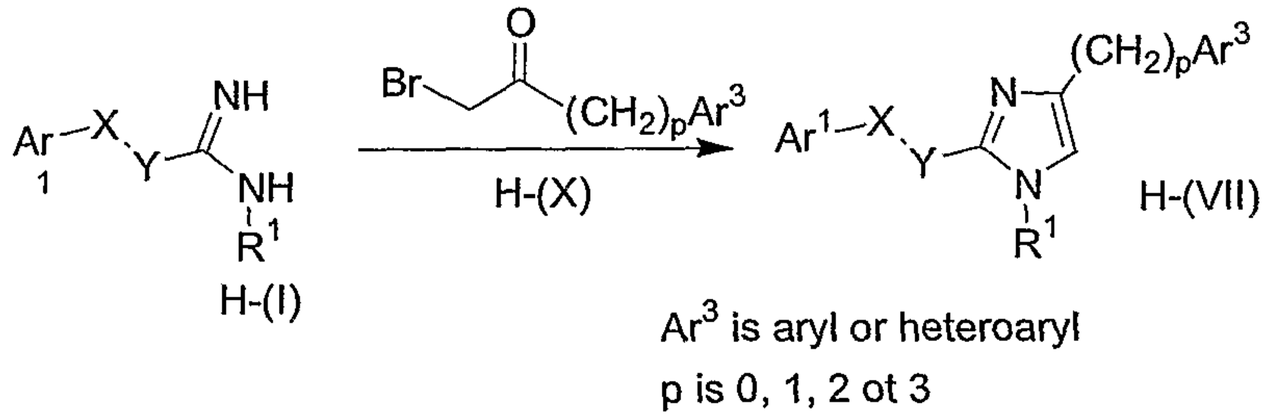
a 4-bromo-3-oxo-butyrate or a 5-bromo-oxo-pentanoate under basic conditions provides the imdiazole ester H- (IIa), which is hydrolyzed to provide the corresponding acid derivative H- (IIb).

Scheme H-2



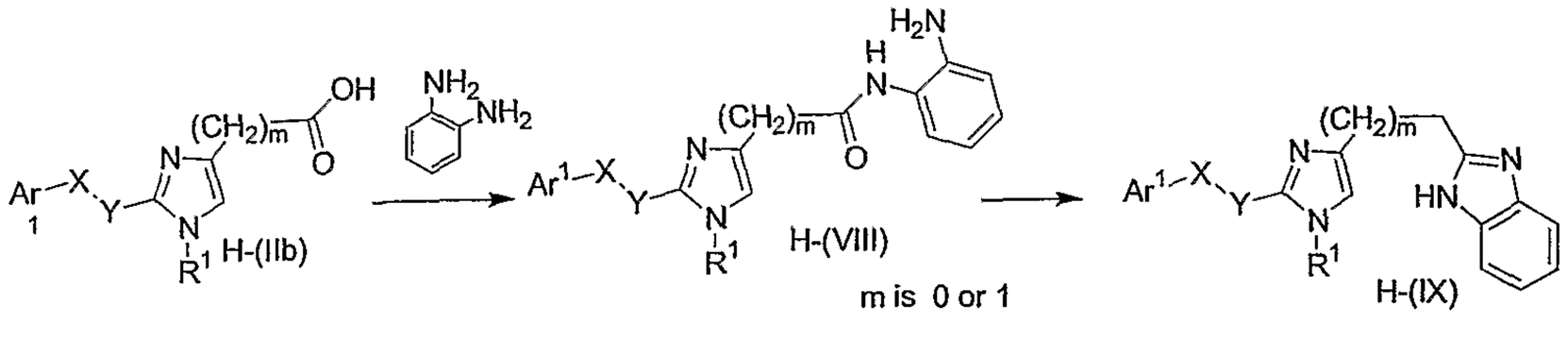
Reaction of the acid H- (IIb) with the appropriately substituted amine under standard coupling procedures provides the desired amide H- (III). Reduction of the amide with common reducing agents such as diborane or lithium aluminum hydride provides the corresponding amine H- (IV). Alternatively treatment of the acid H- (IIb) with Weinreb's reagent provides amide H- (V). Treatment of the amide under standard condition with an organometallic reagent (ex. aryl lithium or aryl magnesium halide) provides the ketone H- (VI). Reduction of the ketone under a variety of conditions affords the desired product H-(VII).

Scheme H-3



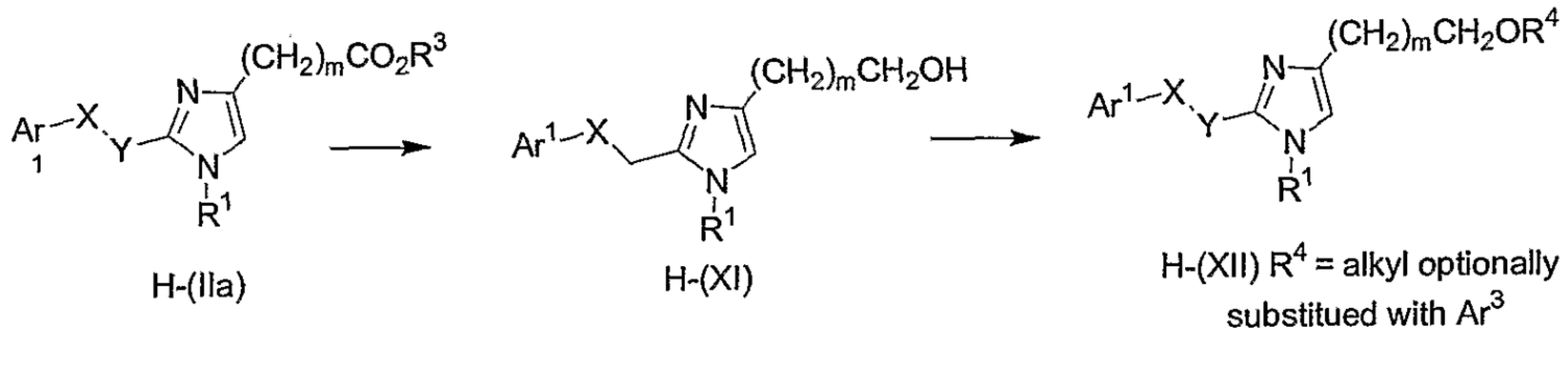
Alternatively treatment of amidine H- (I) with H- (X) provides the desired imidazole H- (VII).

Scheme H-4



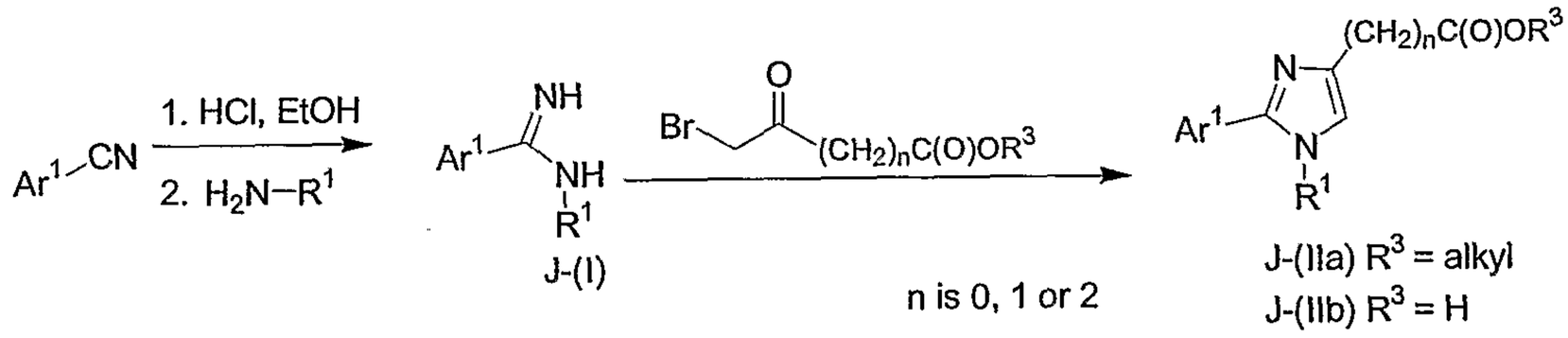
An alternative route to obtain heteroaryl derivatives is to react the activated acid of H-(IIb) with the appropriate substrate followed by cyclization to provide the desired product. For example as depicted in Scheme 4, reaction of the activated acid of H- (IIb) with benzene-1,2-diamine provides the intermediate amide H- (VIII), which is cyclized to afford the benzimidazole derivative H- (IX).

Scheme H-5



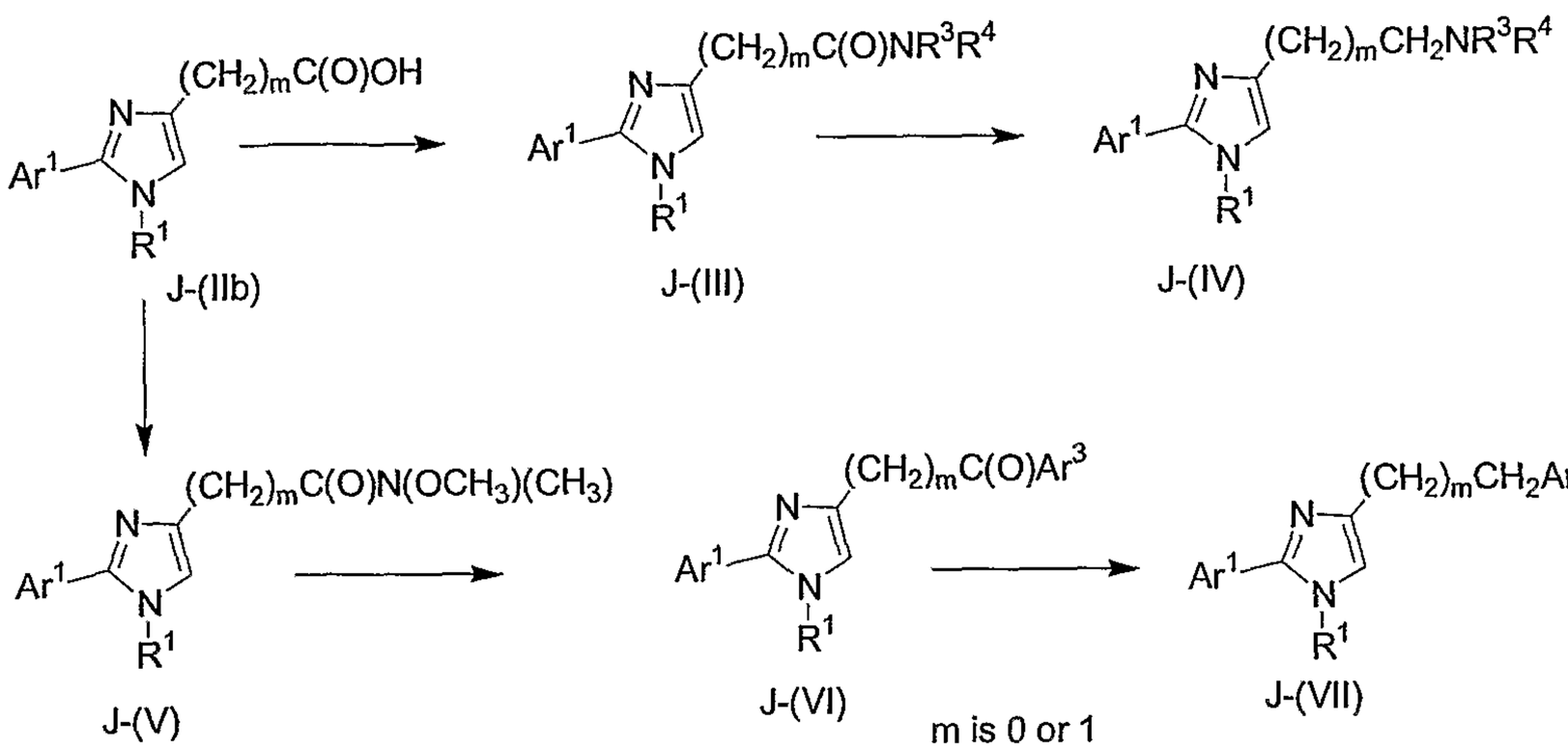
Treatment of carboxylic acid (H-IIa under standard reducing conditions (e.g., lithium conditions (e.g., NaH, halo-R^4) reactions gives H- (XII).

Scheme J-1



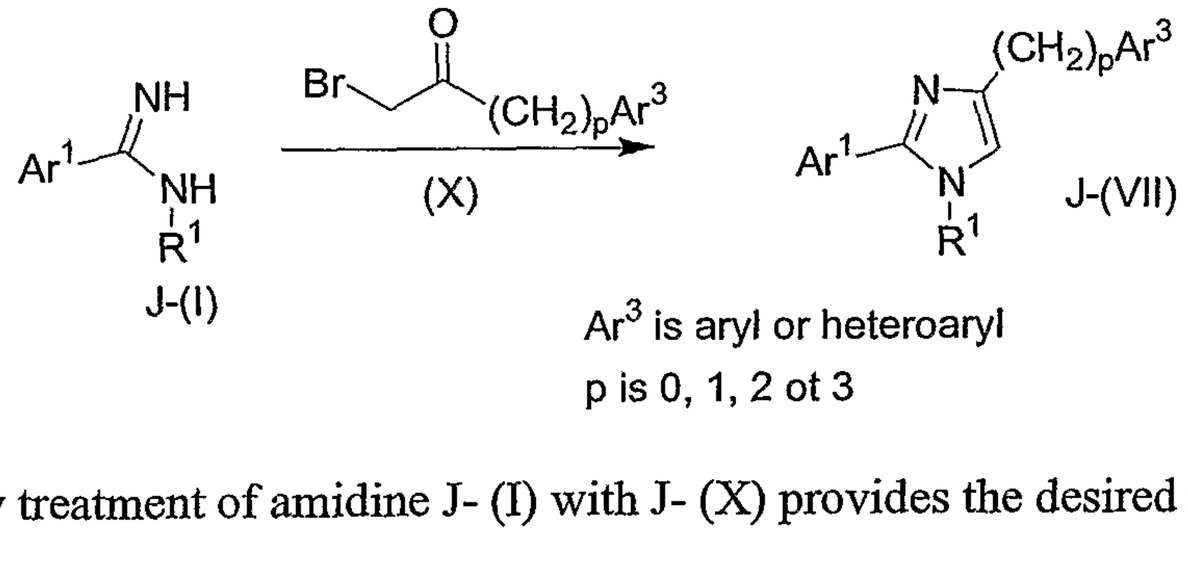
Treatment of an aryl nitrile with an alcohol under acidic conditions provides the alkoxy imidate intermediate, which is treated with the appropriate substituted amine under catalytic conditions (e.g., ethanolic HCl; CuCl; Ln(III) ions) to provide the substituted amidine J- (I). Treatment of amidine J- (I) with a bromopyruvate, a 4-bromo-3-oxo-butyrate, a 5-bromo-4-oxo-pentanoate or a 6-bromo-5-oxo-hexanoate under basic conditions provides the corresponding imidiazole ester J- (IIa), which is hydrolyzed to provide the corresponding acid derivative J- (IIb).

Scheme J-2



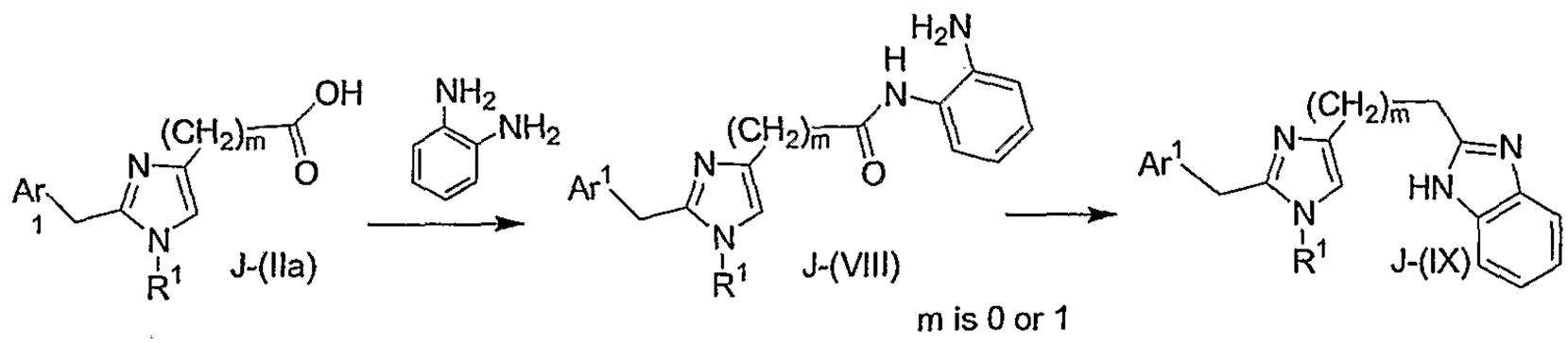
Reaction of the acid J- (IIb) with the appropriately substituted amine under standard coupling procedures provides the desired amide J- (III). Reduction of the amide with common reducing agents such as diborane or lithium aluminum hydride provides the corresponding amine J- (IV). Alternatively treatment of the acid J- (IIb) with Weinreb's reagent provides amide J- (V). Treatment of the amide under standard condition with an organometallic reagent (ex. aryl lithium or aryl magnesium halide) provides the ketone J- (VI). Reduction of the ketone under a variety of conditions affords the desired product J- (VII).

Scheme J-3



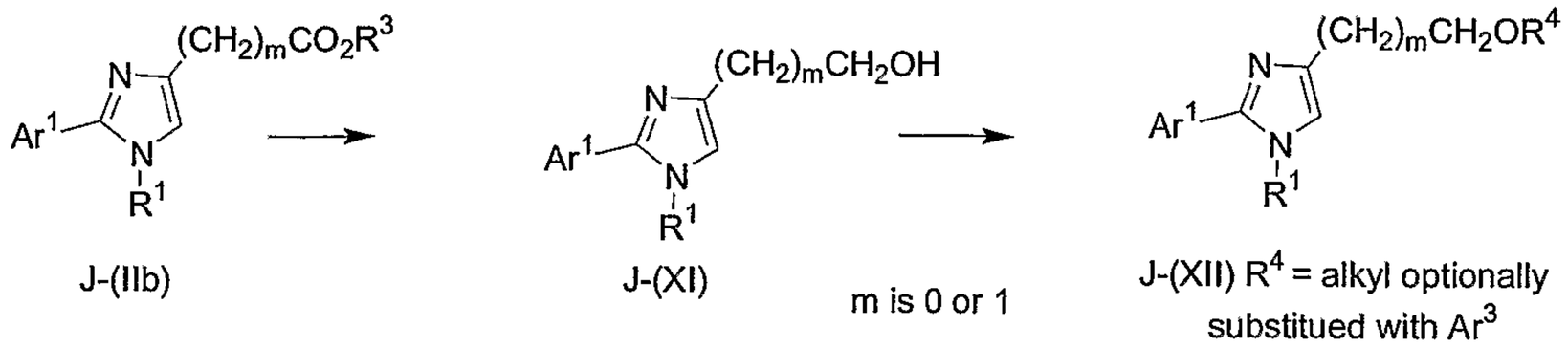
Alternatively treatment of amidine J- (I) with J- (X) provides the desired imidazole J- (VII).

Scheme J-4



An alternative route to obtain heteroaryl derivatives is to react the activated acid of J- (IIb) with the appropriate substrate followed by cyclization to provide the desired product. For example as depicted in Scheme J-4, reaction of the activated acid of J- (IIb) with benzene-1,2-diamine provides the intermediate amide J- (VIII), which is cyclized to afford the benzimidazole derivative J- (IX).

Scheme J-5



Treatment of carboxylic acid J- (IIb) under standard reducing conditions (e.g., lithium aluminum hydride) gives J- (XI). Treatment of J- (XI) under standard ether forming conditions (e.g., NaH, halo-R^4) gives J- (XII).

Compounds are prepared in a manner essentially as described above and in the general schemes.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be

performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, 2nd. Ed., Wiley-VCH Publishers (1999); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1999); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

As used herein, the compounds of this invention, including the compounds of formulae described herein, are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. See, e.g., Alexander, J. et al. *Journal of*

Medicinal Chemistry **1988**, *31*, 318-322; Bundgaard, H. *Design of Prodrugs*; Elsevier: Amsterdam, 1985; pp 1-92; Bundgaard, H.; Nielsen, N. M. *Journal of Medicinal Chemistry* **1987**, *30*, 451-454; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Publ.: Switzerland, 1991; pp 113-191; Digenis, G. A. et al. *Handbook of Experimental Pharmacology* **1975**, *28*, 86-112; Friis, G. J.; Bundgaard, H. *A Textbook of Drug Design and Development*; 2 ed.; Overseas Publ.: Amsterdam, 1996; pp 351-385; Pitman, I. H. *Medicinal Research Reviews* **1981**, *1*, 189-214; Sinkula, A. A.; Yalkowsky. *Journal of Pharmaceutical Sciences* **1975**, *64*, 181-210; Verbiscar, A. J.; Abood, L. G *Journal of Medicinal Chemistry* **1970**, *13*, 1176-1179; Stella, V. J.; Himmelstein, K. J. *Journal of Medicinal Chemistry* **1980**, *23*, 1275-1282; Bodor, N.; Kaminski, J. J. *Annual Reports in Medicinal Chemistry* **1987**, *22*, 303-313.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-$(alkyl)_4^+$ salts. This invention also envisions the

quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The compounds of the formulae described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The compositions delineated herein include the compounds of the formulae delineated herein, as well as additional therapeutic agents if present, in amounts effective for achieving a modulation of disease or disease symptoms, including ion channel-mediated disorders or symptoms thereof. References which include examples of additional therapeutic agents are: 1) *Burger's Medicinal Chemistry & Drug Discovery* 6th edition, by Alfred Burger, Donald J. Abraham, ed., Volumes 1 to 6, Wiley Interscience Publication, NY, 2003; 2) *Ion Channels and Disease* by Francis M. Ashcroft, Academic Press, NY, 2000; and 3) *Calcium Antagonists in Clinical Medicine* 3rd edition, Murray Epstein, MD, FACP, ed., Hanley & Belfus, Inc., Philadelphia, PA, 2002. Additional therapeutic agents include but are not limited to agents for the treatment of cardiovascular disease (e.g., hypertension, angina, atrial fibrillation, prevention of stroke, heart failure, acute myocardial ischemia, etc), metabolic disease (e.g., syndrome X, diabetes, obesity), renal or genito-urinary disease (e.g, glomerular nephritis, urinary incontinence, nephrotic syndrome), and their disease symptoms. Examples of additional therapeutic agents for treatment of cardiovascular disease and disease symptoms include but are not limited to antihypertensive agents, ACE inhibitors, angiotensin II receptor antagonists, statins, β-blockers, antioxidants, anti-inflammatory drugs, anti-thrombotics, anti-coagulants or antiarrythmics. Examples of additional therapeutic agents for treatment of metabolic disease and disease symptoms include but are not limited to ACE inhibitors, angiotensin II antagonists, fibrates, thiazolidinediones or sulphonylurea anti-diabetic drugs. Examples of additional therapeutic agents for treatment of renal and/or genitor-urinary syndromes and their symptoms include but are not limited to alpha-1 adrenergic antagonists (e.g., doxazosin), anti-muscarinics (e.g., tolterodine), norepinephrine/serotonin reuptake inhibitors (e.g., duloxetine), tricyclic antidepressants (e.g., doxepin, desipramine) or steroids.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery

systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium

chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of

the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A composition having the compound of the formulae herein and an additional agent (e.g., a therapeutic agent) can be administered using an implantable device. Implantable devices and related technology are known in the art and are useful as delivery systems where a continuous, or timed-release delivery of compounds or compositions delineated herein is desired. Additionally, the implantable device delivery system is useful for targeting specific points of compound or composition delivery (e.g., localized sites, organs). Negrin et al., Biomaterials, 22(6):563 (2001). Timed-release technology involving alternate delivery methods can also be used in this invention. For example, timed-release formulations based on polymer technologies, sustained-release techniques and encapsulation techniques (e.g., polymeric, liposomal) can also be used for delivery of the compounds and compositions delineated herein.

Also within the invention is a patch to deliver active chemotherapeutic combinations herein. A patch includes a material layer (e.g., polymeric, cloth, gauze, bandage) and the compound of the formulae herein as delineated herein. One side of the material layer can have a protective layer adhered to it to resist passage of the compounds or compositions. The patch can additionally include an adhesive to hold the patch in place on a subject. An adhesive is a composition, including those of either

natural or synthetic origin, that when contacted with the skin of a subject, temporarily adheres to the skin. It can be water resistant. The adhesive can be placed on the patch to hold it in contact with the skin of the subject for an extended period of time. The adhesive can be made of a tackiness, or adhesive strength, such that it holds the device in place subject to incidental contact, however, upon an affirmative act (e.g., ripping, peeling, or other intentional removal) the adhesive gives way to the external pressure placed on the device or the adhesive itself, and allows for breaking of the adhesion contact. The adhesive can be pressure sensitive, that is, it can allow for positioning of the adhesive (and the device to be adhered to the skin) against the skin by the application of pressure (e.g., pushing, rubbing,) on the adhesive or device.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The invention will be further described in the following examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Example A1

Oocyte Assay

Representative compounds of the formulae herein are screened for activity against calcium channel targets in an assay essentially as described in *Neuron* January 1997, 18(11): 153-166, Lin *et. al.*; *J. Neurosci.* July 1, 2000,20(13):4768-75, J. Pan and D. Lipsombe; and *J. Neurosci.*, August 15, 2001, 21(16):5944-5951, W. Xu and D. Lipscombe, using *Xenopus oocyte* heterologeous expression system. The assay is performed on various calcium channels (e.g., $Ca_V1.2$ or $Ca_V1.3$ subfamily) whereby the modulation of the calcium channel is measured for each compound.

Example A2

HEK Assay

HEK-293T/17 cells are transiently transfected in a similar manner as described in FuGENE 6 Package Insert Version 7, April 2002, Roche Applied Science, Indianapolis, IN. The cells are plated at 2.5 x 10^5 cells in 2 mL in a 6-well plate in incubator for one night and achieve a 30~40% confluence. In a small sterile tube, add sufficient serum-free medium as diluent for FuGENE Transfection Reagent (Roche Applied Science, Indianapolis, IN), to a total volume of 100 µL. Add 3 µL of FuGENE 6 Reagent directly into this medium. The mixture is tapped gently to mix. 2 µg of DNA solution (0.8-2.0 µg/µL) is added to the prediluted FuGENE 6 Reagent from above. The DNA/Fugene 6 mixture is gently pipeted to mix the contents and incubated for about 15 minutes at room temperature. The complex mixture is then added to the HEK-293T/17 cells, distributing it around the well, and swirled to ensure even dispersal. The cells are returned to the incubator for 24hrs. The transfected cells are then replated at density 2.5X10^5 in a 35mm dish with 5 glass coverslips and grow in low serum(1%) media for 24hrs. Coverslips with isolated cells are then transferred into chamber and calcium channel (e.g., L-type, N-type, etc.) current or other currents for counter screening are recorded from the transiently transfected HEK-293T/17 cells.

The whole-cell voltage clamp configuration of the patch clamp technique is employed to evaluate voltage-dependent calcium currents essentially as described by Thompson and Wong (1991) *J. Physiol.,* 439: 671-689. To record calcium channel (e.g., L-type, N-type, etc.) currents for evaluation of inhibitory potency of compounds (steady-state concentration-response analysis), five pulses of 20-30 ms voltage steps to about +10 mV (the peak of the current voltage relationship) are delivered at five Hz every 30 second from a holding potential at -100mV. Compound evaluations were carried out essentially as described by Sah DW and Bean BP (1994) *Mol Pharmacol.*45(1):84-92.

Example A3

Formalin Test

Representative compounds of the formulae herein are screened for activity in the formalin test. The formalin test is widely used as a model of acute and tonic inflammatory pain (Dubuisson & Dennis, 1977 *Pain* 4:161-174; Wheeler-Aceto et al,

1990, *Pain* 40:229-238; Coderre et al, 1993, *Pain* 52:259-285). The test involves the administration to the rat hind paw of a dilute formalin solution followed by monitoring behavioral signs (i.e., flinching, biting and licking) during the "late phase" (11 to 60 minutes post injection) of the formalin response which reflects both peripheral nerve activity and central sensitization.. Male, Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing approximately 225-300 g are used with an n=6-8 for each treatment group.

Depending on pharmacokinetic profile and route of administration, vehicle or a dose of test compound is administered to each rat by the intraperitoneal or oral route 30-120 minutes prior to formalin. Each animal is acclimated to an experimental chamber for 60 minutes prior to formalin administration, which is 50μL of a 5% solution injected subcutaneously into the plantar surface of one hind paw using a 300μL microsyringe and a 29 gauge needle. A mirror is angled behind the chambers to enhance the views of the animals' paws. The number of flinches (paw lifts with or without rapid paw shaking) and the time spent biting and/or licking the injured hind paw are recorded for each rat for 2 continuous minutes every 5 minutes for a total of 60 minutes after formalin administration. A terminal blood sample is harvested for analysis of plasma compound concentrations. Between groups comparisons of the total number of flinches or time spent biting and/or licking during the early or late phase are conducted using one-way analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant and $p = 0.05$-1.0 was considered evidence of a statistical trend. Data were presented graphically as mean ± S.E.M. for each 5-minute interval of the 60-minute experimental observation period. Compounds were considered efficacious based on their ability to inhibit the number of flinches or the time spent biting and/or licking during the late phase of the formalin response. Representative compounds of the formulae herein are evaluated for activity against calcium channel targets.

Representative compounds of the formulae herein were evaluated for activity against calcium channel targets.

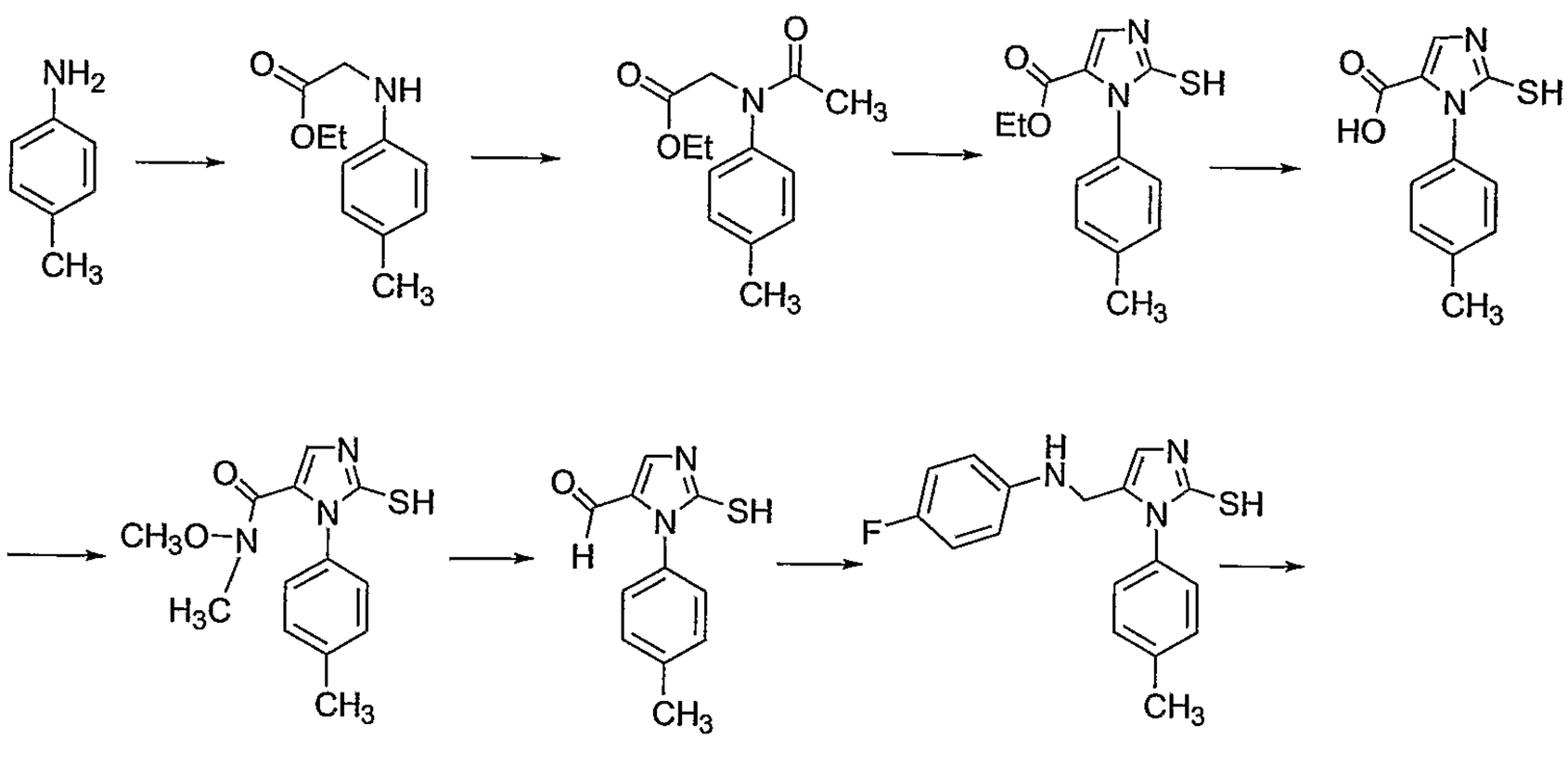
Example A4

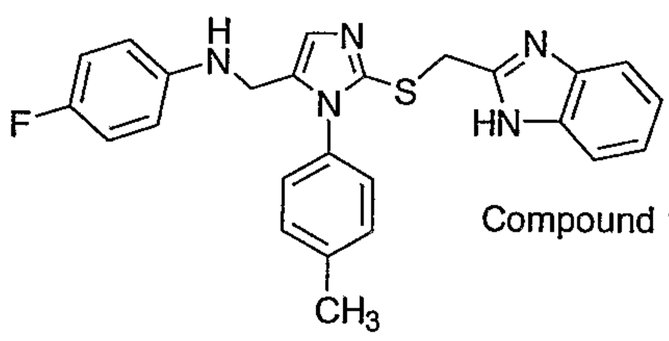
Method A

Compound A1 (compound 1 of Scheme A5)

{2-[2-(1H-Benzoimidazol-2-yl)-ethylsulfanyl]-3-p-tolyl-3H-imidazol-4-ylmethyl}-(4-fluoro-phenyl)-amine

Scheme A5





Part 1. Preparation of p-Tolylamino-acetic acid ethyl ester

A mixture of p-toluidine (16.6 g, 155 mmol), sodium acetate (16.5 g, 201.5 mmol) in ethanol (200 mL) was stirred and ethyl bromoacetate (16.5 mL, 155 mmol) was added at room temperature. The mixture was heated at 80 °C for 1 hour then cooled to room temperature. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The resulting residue was purified by chromatography (SiO_2, 20% ethyl acetate in n-hexane to give p-tolylamino-acetic acid ethyl ester (23.9 g, 124 mmol) as a white solid.

Part 2. Prepartion of (Acetyl-p-tolyl-amino)-acetic acid ethyl ester

A cooled solution of p-tolylamino-acetic acid ethyl ester (23.9 g, 124mmol) in THF (300 mL) was stirred and acetyl chloride (10.5 mL, 148 mmol) was slowly added. The mixture was stirred for 1 hour and quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give (acetyl-p-tolyl-amino)-acetic acid ethyl ester (14.3 g, 96 mmol) as a white solid.

Part 3. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid ethyl ester

A solution of p-tolylamino-acetic acid ethyl ester (5.0 g, 21.3) and ethyl formate (5.3 g, 71.3 mmol) in benzene (10 mL) was cooled to 0 °C and potassium ethoxide (21.3 mmol) was added. The mixture was placed in a refrigerator to stand overnight and was extracted with water. To the aqueous solution was added potassium thiocyanate (2.14 g, 22.0 mmol) and concentrated aqueous HCl (4 mL). The mixture was heated for 2 hours at 60 °C then cooled. The mixture was extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid ethyl ester (1.7 g, 6.5 mmol) as a white solid.

Part 4. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid

A solution of 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid ethyl ester (1.2 g, 4.6 mmol) in 1,4-dioxane (10 mL) was stirred and lithium hydroxide hydrate (1 M, 10 mL) was added and the mixture was stirred at room temperature for 2 hours. The mixture was neutralized with aqueous 2N HCl and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (1 g, 4,3 mmol) as a white solid.

Part 5. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid methoxy-methyl-amide

A mixture of 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (0.468 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.382 g, 2 mmol) and N,O-dimethylhydroxylamine (0.195 g, 2 mmol) in pyridine (4 mL) was

heated at 40 °C overnight. The mixture was cooled, quenched with water and extracted with ethyl acetate. The organics were dried, concentrated under vacuum to give 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid methoxy-methyl-amide (0.245 g, 0.88 mmol) as an oil.

Part 6. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carbaldehyde

A mixture of lithium aluminum hydride (0.10 g, 2.65 mmol) in tetrahydrofuran (10 mL) was stirred under nitrogen blanket at 0 °C and 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid methoxy-methyl-amide (0.245 g, 0.88 mmol) in THF (5 mL) was added. The mixture was allowed to warm to room temperature and stir for 2 hours. The mixture was cooled to 0 °C and quenched with aqueous 15% sodium bicarbonate and water then extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give 2-mercapto-3-p-tolyl-3H-imidazole-4-carbaldehyde (0.176 g, 0.80 mmol) as a solid.

Part 7. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide

A solution of 2-mercapto-3-p-tolyl-3H-imidazole-4-carbaldehyde (0.176 g, 0.80 mmol) and 4-fluoroaniline (0.80 mmol, 88 mgs) in DMF/acetic acid (10/1:v/v, 3 mL) was stirred at room temperature for 1 hour. Sodium cyanoborohydride (0.76 g, 1.2 mmol) was added and the mixture stirred overnight. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated to give a residue. Purification by chromatography (SiO_2, 5% methanol in methylene chloride) gave 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (0.05g, 0.16 mmol) as a solid.

Part 8. Preparation of 2-[2-(1H-Benzoimidazol-2-yl)-ethylsulfanyl]-3-p-tolyl-3H-imidazol-4-ylmethyl}-(4-fluoro-phenyl)-amine

A mixture of 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (0.05 g, 0.16 mmol)) and 2-(chloromethyl)benzimidazole (0.032 g, 0.19 mmol) in acetone (5 mL) was stirred and potassium carbonate (0.048 g, 0.35 mmol) was

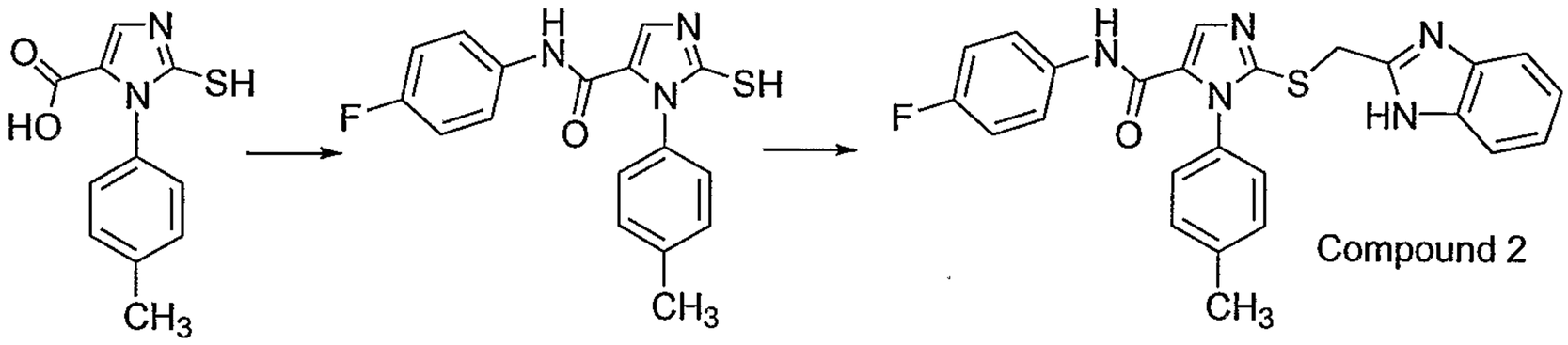
added. The mixture was heated at 40 °C for 2 hours and cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a solid. The solid was dissolved in diethyl ether and a solution of etheral-HCl was added. The mixture was concentrated under vacuum to give 2-[2-(1H-Benzoimidazol-2-yl)-ethylsulfanyl]-3-p-tolyl-3H-imidazol-4-ylmethyl}-(4-fluoro-phenyl)-amine (0.042 g, 0.08 mmol) as the HCl salt.

Method B

Compound 2 (compound 2 of Scheme A2)

2-(1H-Benzoimidazol-2-ylmethylsulfanyl)-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide

Scheme A2



Part 1. Preparation of 2-Mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide

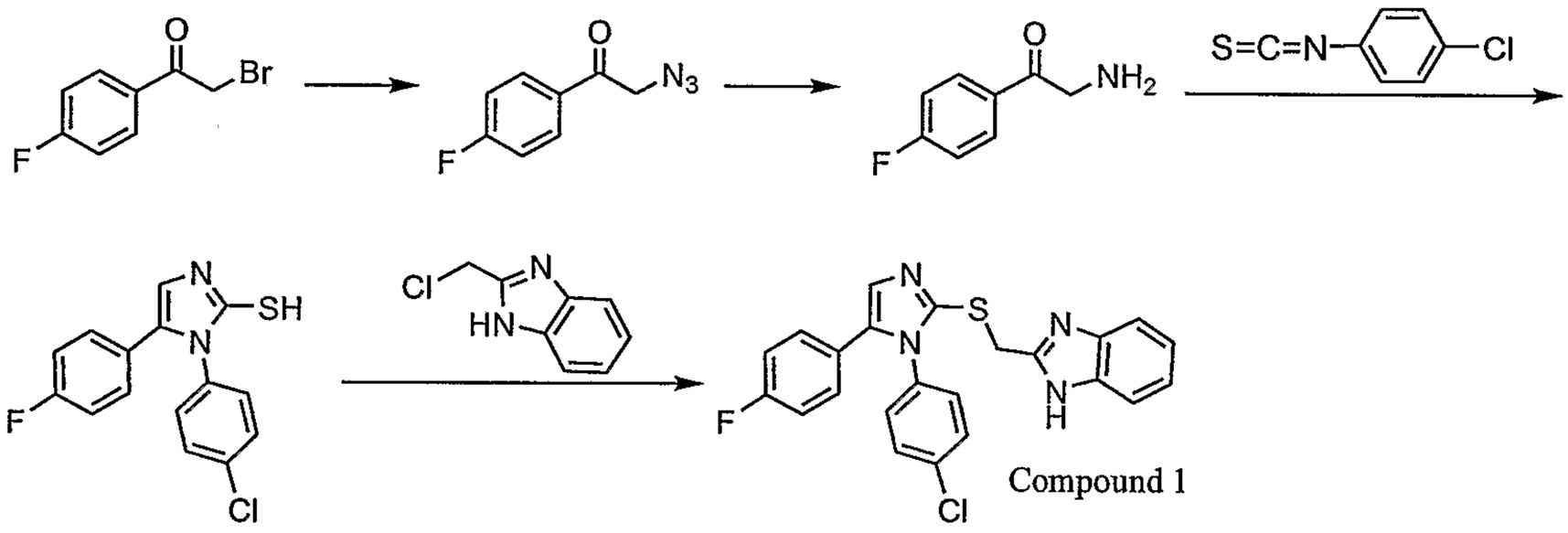
A mixture of 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (0.468 g, 2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.382 g, 2 mmol) and 4-fluoroaniline (0.222 g, 2 mmol) in pyridine (4 mL) was heated at 40 °C overnight. The mixture was cooled and quenched with water and extracted with ethyl acetate. The organics were dried, concentrated under vacuum to give 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (0.206 g, 0.63 mmol) as an oil.

Part 2. Preparation of 2-(1H-Benzoimidazol-2-ylmethylsulfanyl)-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide

To a solution of 2-mercapto-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (0.206 g, 0.63 mmol) and 2-(chloromethyl)benzimidazole (0.166 g, 1.00 mmol) in acetone (10 mL) was stirred and potassium carbonate (0.191 g, 1.12 mmol) was added. The mixture was heated at 40 °C for 2 hours and cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a solid. Purification by chromatography (SiO_2, 20% acetone in n-hexane) gave 2-(1H-benzoimidazol-2-ylmethylsulfanyl)-3-p-tolyl-3H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (0.133 g, 0.29 mmol) as a white solid.

Example B4

Scheme B2



Compound 1 (compound 1 of Scheme B2)

2-[1-(4-Chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazol-2-ylsulfanylmethyl]-1H-benzoimidazole

Part 1. Preparation of 2-Azido-1-(4-fluoro-phenyl)-ethanone

A solution of 2-bromo-1-(4-fluoro-phenyl)-ethanone (2.5 g, 11.5 mmol) in DMSO (15 mL) at 10 °C was vigorously stirred and sodium azide (0.94 g, 14.4 mmol) was added. The mixture was stirred for 1 hour then quenched with water (20 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered and

concentrated under reduce pressure to give 2-azido-1-(4-fluoro-phenyl)-ethanone (1.7 g, 9.3 mmol) as a viscous yellow-red liquid.

Part 2. Preparation of 2-Amino-1-(4-fluoro-phenyl)-ethanone hydrochloride

To a solution of 2-azido-1-(4-fluoro-phenyl)-ethanone (8.0 g, 44.7 mmol) in ethanol (125 mL) was added concentrated aqueous HCl (6 mL) and 10% Pd/C (10 mol %). The mixture was stirred under hydrogen (H_2) atmosphere at 45 psi for 1 hour. The mixture was filtered through celite and the celite cake was washed with copious amounts of methanol. The solvent was under reduce pressure and the semisolid was triturated with diethyl ether, filtered and dried to give 2-amino-1-(4-fluoro-phenyl)-ethanone hydrochloride (5.0 g, 26.5 mmol) as a white crystalline solid.

Part 3. Preparation of 1-(4-Chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol

A mixture of 2-amino-1-(4-fluoro-phenyl)-ethanone hydrochloride (5.0 g, 26.5 mmol), 4-chlorophenyl isothiocyanate (4.49 g, 26.5 mmol) and sodium hydrogencarbonate (3.3 g, 39.7 mmol) in ethanol (100 mL) was heated at 90 °C for 2 hours. The solvent was removed under reduce pressure. The resulting residue was re-suspended in aqueous 1N sodium hydroxide (50 mL) and heated at 100 °C overnight. The hot mixture was filtered, cooled and carefully acidifed with aqueous 6N HCl. The resulting mixture was filtered to give 1-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol (8.0 g, 26.3 mmol) as a yellow solid after drying.

Part 4. Preparation of 2-[1-(4-Chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazol-2-yl-sulfanylmethyl]-1H-benzoimidazole

A mixture of 1-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol (4.0 g, 13.2 mmol), 2-(chloromethyl)benzimidazole (2.2 g, 13.2 mmol) and potassium carbonate (5.5 g, 39.6 mmol) in acetone (50 mL) was heated at 75 °C until all starting materials were consumed. The mixture was cooled and the solvent was removed under reduce pressure. The resulting residue was partitioned in 1:1:1 water/ethyl acetate/hexane. The brown solid was filtered, dried and re-suspended in minimal amount of methanol. The methanolic mixture was filtered and dried to obtain a white

solid. The solid was re-suspended in methanol and treated with ethereal 2N HCl until a solution persisted. The solution was diluted with a large amount of diethyl ether to promote precipitation, filtered and dried to give 2-[1-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazol-2-yl-sulfanylmethyl]-1H-benzoimidazole (3.5 g, 7.4 mmol) as a white solid.

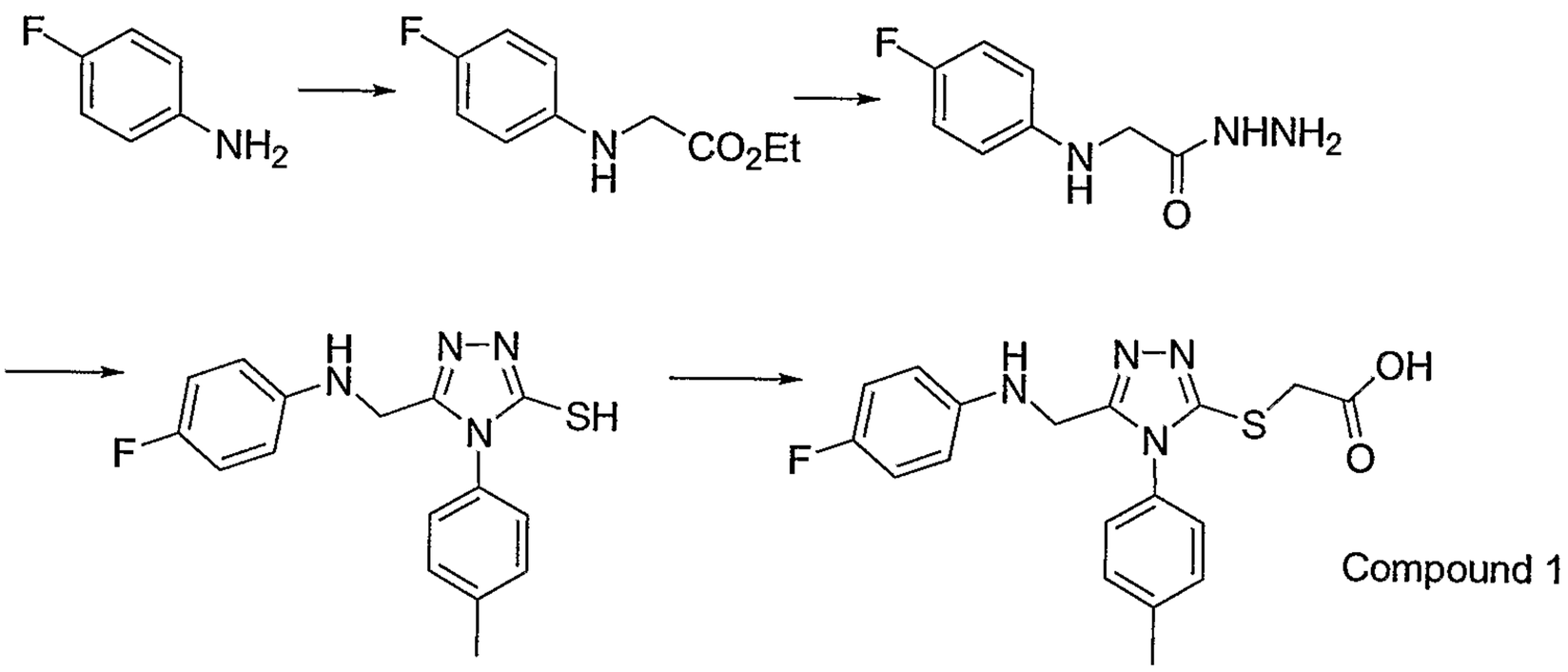
Example C4

Method CA

Compound C1 (compound 1 in Scheme C4)

{5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid

Scheme C4



Compound 1

Part 1. Preparation of (4-Fluoro-phenylamino)-acetic acid ethyl ester

A mixture of 4-fluoroaniline (10 g, 90 mmol), bromoacetate (15 g, 90 mmol), and sodium acetate (11 g, 135 mmol) in ethanol (200 mL) was heated reflux for 2 hours. The cooled reaction was cooled and concentrated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give (4-fluoro-phenylamino)-acetic acid ethyl ester (8.46 g, 42.9 mmol) as a white solid.

Part 2. Preparation of (4-Fluoro-phenylamino)-acetic acid hydrazide

A mixture of (4-fluoro-phenylamino)-acetic acid ethyl ester and hydrazine (8.23 g, 257 mmol) in ethanol (200 mL) was refluxed for 3 hours. The reaction was cooled and concentrated under vacuum. Trituration of the residue with n-hexane (75 mL) gave (4-fluoro-phenylamino)-acetic acid hydrazide (5.5 g, 30.20 mmol) as a white solid.

Part 3. Preparation of 5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

A mixture of (4-fluoro-phenylamino)-acetic acid hydrazide and p-Tolueneisothiocyanate (4.5 g, 30.20 mmol) in aqueous 2N sodium hydroxide (100 mL) and heated for several hours then cooled. The solution was neutralized with 6N hydrochloric acid and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a brown residue. Trituration of the residue with n-hexane (100mL) gave 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (7.6 g, 24.2 mmol) as a white solid.

Part 4. Preparation of {5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid

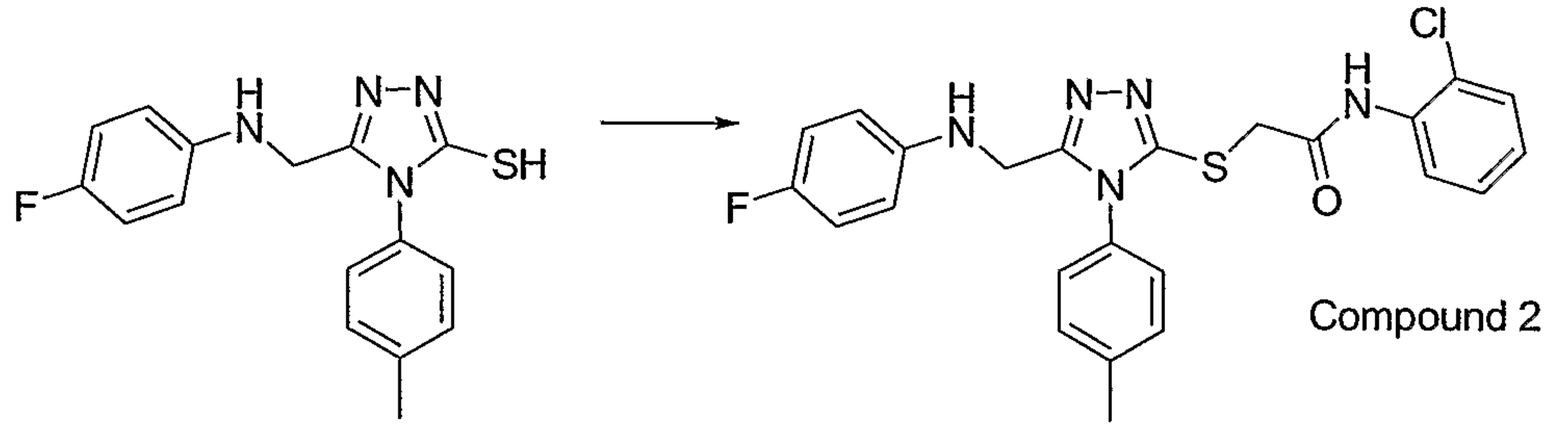
To a mixture of 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.30 gm, 0.95 mmol), bromoacetic acid (0.13 gm, 0.95 mmol) and potassium carbonate (0.16 gm, 1.14 mmol) in acetone (6 mL) was heated at 40C for 3 hours then cooled. The reaction was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a residue. The residue was purified by chromatography on silica (20% methanol in methylene chloride) to give {5-[(4-Fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetic acid (0.27 gm, 0.72 mmol) as a white solid.

Method CB

Compound C2 (compound 2 in Scheme C5)

N-(2-Chloro-phenyl)-2-{5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide

Scheme C5



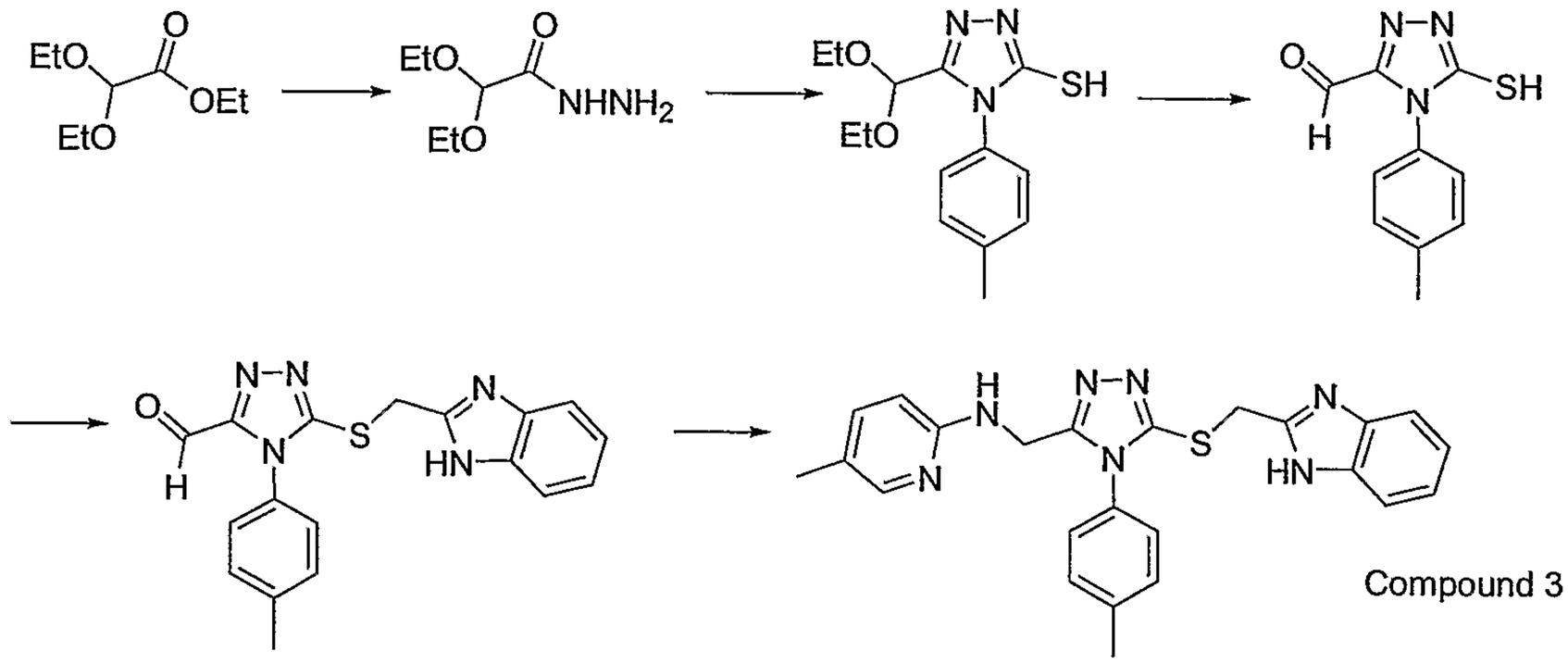
Part 1. Preparation of N-(2-Chloro-phenyl)-2-{5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide

To a mixture of 5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.30 gm, 0.95 mmol), 2-bromo-N-(2-chloro-phenyl)-acetamide (0.24 gm, 0.95 mmol) and potassium carbonate (0.16 gm, 1.14 mmol) in acetone (6 mL) was heated at 40C for 3 hours then cooled. The reaction was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a residue. The residue was purified by chromatography on silica (20% methanol in methylene chloride) to give N-(2-Chloro-phenyl)-2-{5-[(4-fluoro-phenylamino)-methyl]-4-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl}-acetamide (0.10 gm, 0.20 mmol) as a white solid.

Method CC

Compound C3 (compound 3 in Scheme C6)

Scheme C6



[5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine

Part 1. Preparation of Diethoxy-acetic acid hydrazide

A solution of ethyl diethoxyacetate (15.8 g, 90 mmol) ethanol (100 mL) was stirred and hydrazine(8.23 g, 257 mmol) was added. The mixture was heated at reflux for 2 hours. then cooled and concentrated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give diethoxy-acetic acid hydrazide (10.53 g, 65 mmol) as a clear oil.

Part 2. Preparation of 5-Diethoxymethyl-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

p-Tolueneisothiocyanate (9.7 g, 65mmol) and diethoxy-acetic acid hydrazide (10.53 g, 65 mmol) was dissolved in aqueous 2N sodium hydroxide (100 mL) and heated for several hours then cooled. The solution was neutralized with 6N hydrochloric acid and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a yellow residue. Trituration of the residue with n-hexane (100mL) gave 5-diethoxymethyl-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (12.3 g, 42mmol) as a yellow solid.

Part 3. Preparation of 5-Thioxo-4-p-tolyl-4,5-dihydro-1H-[1,2,4]triazole-3-carbaldehyde

A solution of 5-diethoxymethyl-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (5 g, 17 mmol) and Aqueous 3N HCl (30 mL) in 1,4-dioxane (10 mL) was stirred and heated at 40C for 2 hours then cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO_2, 10% acetone in n-hexane) gave 5-thioxo-4-p-tolyl-4,5-dihydro-1H-[1,2,4]triazole-3-carbaldehyde (2.6 g, 11.8 mmol) as a yellow solid.

Part 4. Preparation of 5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazole-3-carbaldehyde

A solution of 5-thioxo-4-p-tolyl-4,5-dihydro-1H-[1,2,4]triazole-3-carbaldehyde (2.6 g, 1.8 mmol) and 2-(chloromethyl)benzimidazole (2.15 g, 12.9 mmol) in acetone (10 mL) was stirred and potassium carbonate (2.07 g, 15 mmol) was added. The mixture was heated at 40C for 3 hours then cooled. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO_2, 30% acetone in n-hexane) gave 5-(1H-benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazole-3-carbaldehyde (2.50 g, 7.08 mmol) as white solid.

Part 5. Preparation of [5-(1H-Benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine

A solution of 5-(1H-benzoimidazol-2-ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazole-3-carbaldehyde (1.0 g, 4.56 mmol) and 2-amino-5-methyl pyridine (0.49 g, 4.56 mmol) in DMF/ HOAc (10/1:v/v) (10 mL) was stirred at room temperature for 1 hour. Sodium cyanoborohydride (0.376 g, 6.0 mmol) was added and mixture was stirred overnight. The mixture was quenched with water and extracted with ethyl acetate. The organics dried and concentrated to give a residue. Purification by flash chromatography (SiO_2, 30% acetone in n-hexane) gave [5-(1H-Benzoimidazol-2-

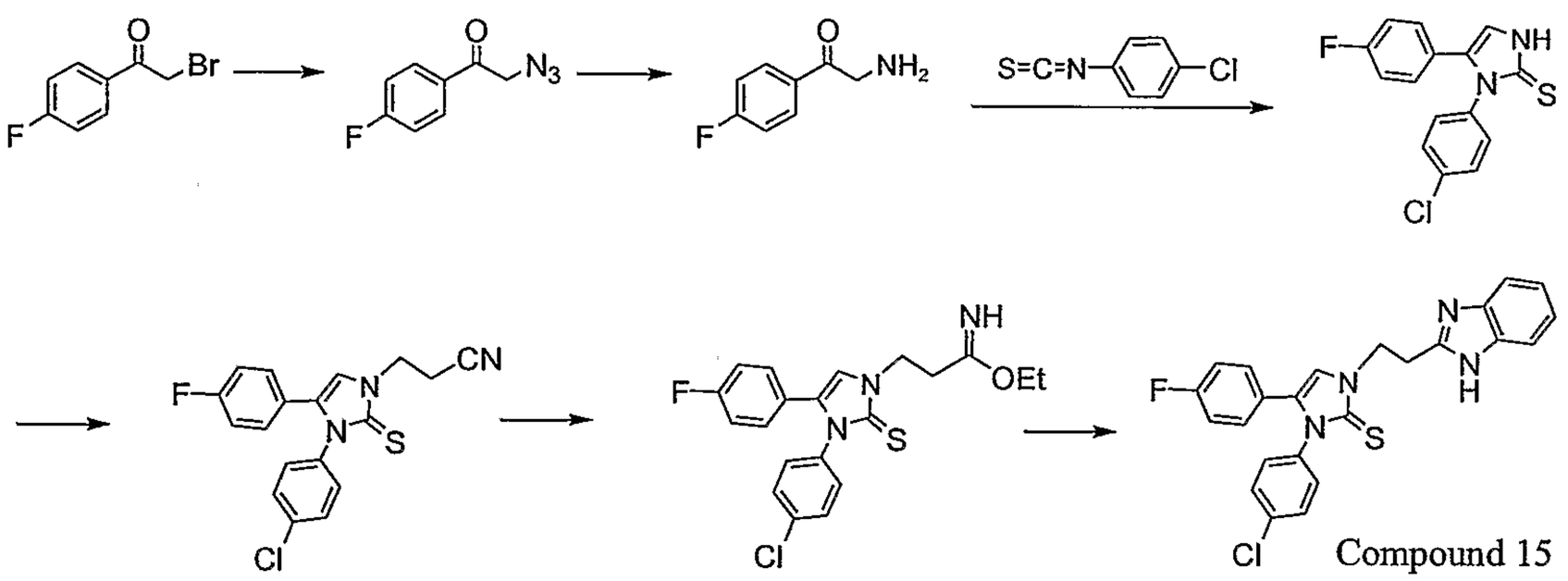
ylmethylsulfanyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-(5-methyl-pyridin-2-yl)-amine (0.108 g, 0.25 mmol) as an off-white solid.

Example D-4

Compound D-15

3-(2-(1H-Benzo[d]imidazol-2-yl)ethyl)-5-(4-fluorophenyl)-1-p-tolyl-1H-imidazole-2(3H)-thione

Scheme D-6



Compound 15

Part 1. Preparation of 2-Azido-1-(4-fluoro-phenyl)-ethanone

A solution of 2-bromo-1-(4-fluoro-phenyl)-ethanone (1 eq) in DMSO at 10 °C is vigorously stirred and sodium azide (1.25 eq) is added. The mixture is stirred for 1 hour then quenched with water and extracted with ethyl acetate (2X). The combined organic layers are washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give 2-azido-1-(4-fluoro-phenyl)-ethanone.

Part 2. Preparation of 2-Amino-1-(4-fluoro-phenyl)-ethanone hydrochloride

To a solution of 2-azido-1-(4-fluoro-phenyl)-ethanone in ethanol is added concentrated HCl (aq) and 10% Pd/C (10 mol %). The mixture is stirred under hydrogen (H_2) atmosphere at 45psi for 1 hour. The mixture is filtered through celite

and the celite cake is washed with copious amounts of methanol. The solvent is removed under reduce pressure and the resulting residue is triturated with diethyl ether, filtered and dried to give 2-amino-1-(4-fluoro-phenyl)-ethanone hydrochloride.

Part 3. Preparation of 1-(4-Chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol

A mixture of 2-amino-1-(4-fluoro-phenyl)-ethanone hydrochloride (1 eq), 4-chlorophenyl isothiocyanate (1 eq) and sodium hydrogencarbonate (1.5 eq) in ethanol is heated at 90 °C for 2 hours. The solvent is removed under reduce pressure. The resulting residue is re-suspended in aqueous 1N sodium hydroxide and heated at 100 °C overnight. The hot mixture is filtered, cooled and carefully acidifed with aqueous 6N HCl. The resulting mixture is filtered to give 1-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol.

Part 4. Preparation of 3-(5-(4-Fluorophenyl)-1,2-dihydro-2-thioxo-1-p-tolylimidazol-3-yl)propanenitrile

A mixture 5-(4-fluorophenyl)-1-p-tolyl-1H-imidazole-2-thiol (1 eq) in dioxane is stirred and Triton B is added. The mixture is heated to 70°C and acrylonitrile (1 eq) is added and heated for 3 hours. The cooled mixture is partitioned between aqueous 0.1N HCl and ethyl acetate. The organic layer is washed with water and brine, dried over sodium sulfate, filtered and the solvent removed under reduce pressure. Flash chromatography (SiO_2) gives 3-(5-(4-fluorophenyl)-1,2-dihydro-2-thioxo-1-p-tolylimidazol-3-yl)propanenitrile.

Part 5. Preparation of 3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionimidic acid ethyl ester

A solution of the propionitrile in 1:1 ethanol/diethylether is cooled in a ice water bath and HCl (g) is carefully bubbled in the solution over 10-20 minutes. The reaction mixture is stirred at room temperature for 2-4 hours and the solvent is

removed under reduce pressure to obtain 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionimidic acid ethyl ester.

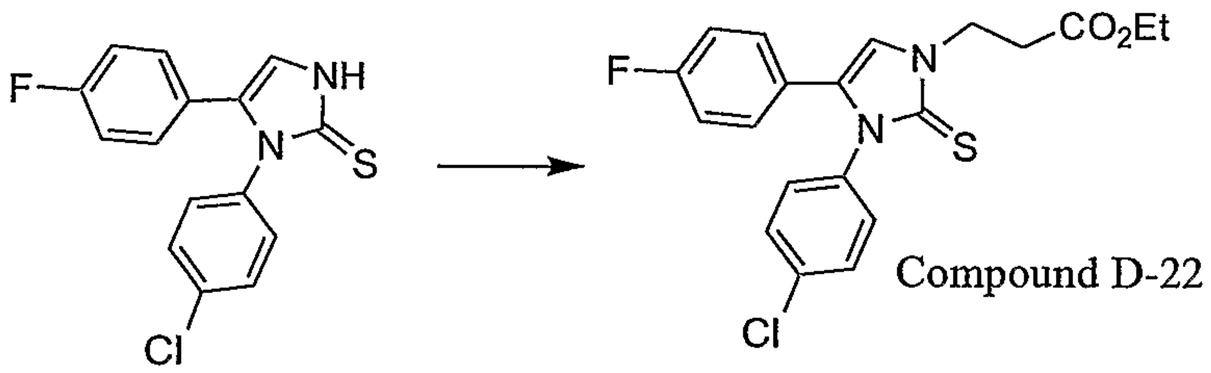
Part 6. Preparation of 3-(2-(1H-Benzo[d]imidazol-2-yl)ethyl)-5-(4-fluorophenyl)-1-p-tolyl-1H-imidazole-2(3H)-thione

A mixture of the propionimidic acid ethyl ester and benzene-1,2-diamine in ethanol is stirred and heated at 60°C overnight. The solvent is removed under reduce pressure; the residue is partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer is dried over sodium sulfate, filtered and the solvent removed under reduce pressure. Purification by flash chromatography (SiO_2) followed by HCl salt formation (methanol and 2M ethereal HCl) gives 3-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-5-(4-fluorophenyl)-1-p-tolyl-1H-imidazole-2(3H)-thione hydrochloride.

Compound D-22

3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid ethyl ester

Scheme D-7



Compound D-22

Preparation of 3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid ethyl ester

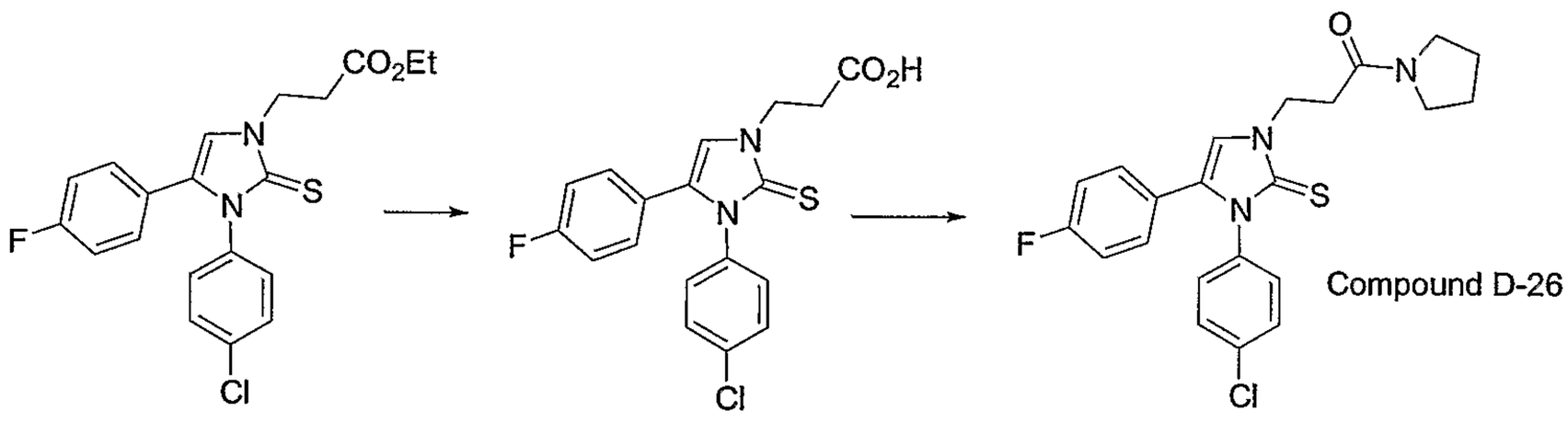
To a solution 1-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazole-2-thiol (1 eq) in DMF is added a 1M solution of lithium bis(trimethylsilyl)amide in THF (1 eq) and ethyl 3-bromopropionate (1 eq) at room temperature. The mixture is heated at 60°C for 2 hours and cooled to room temperature. The mixture is quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under

vacuum. The residue is purified by chromatography on silica to give 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid ethyl ester.

Compound D-26

3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)-1-(pyrrolidin-1-yl)propan-1-one

Scheme D-8



Part 1. Preparation of 3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid

A mixture of 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid ethyl ester (1 eq) and lithium hydroxide hydrate (1.2 eq) is dissolved in 1,4-dioxane: water (4/1:v/v) and allowed to stir at room temperature for 3 hours. The reaction mixture is neutralized with aqueous 2N HCl and extracted with ethyl acetate. The organics are dried and concentrated under vacuum to give 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid.

Part 2. Preparation of 3-(1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)-1-(pyrrolidin-1-yl)propan-1-one

To a solution of 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)propionic acid (1 eq), 1-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.7 eq) and morpholine (1.7 eq) in THF is stirred overnight at room temperature. The reaction is quenched with water and extracted

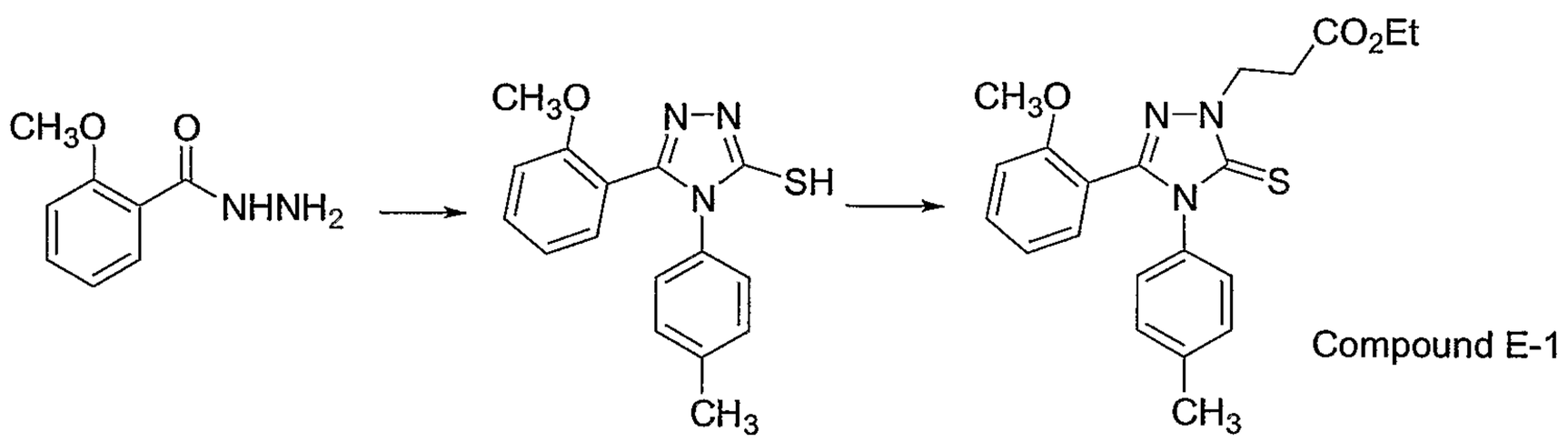
with ethyl acetate. The organics are dried and concentrated under vacuum. The residue is purified by chromatography on silica to give 3-(1-(4-chlorophenyl)-5-(4-fluorophenyl)-1,2-dihydro-2-thioxoimidazol-3-yl)-1-(pyrrolidin-1-yl)propan-1-one.

Example E-4

Compound E-1

3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid, ethyl ester

Scheme E-5



Part 1. Preparation of 5-(2-Methoxy-phenyl)-4-p-tolyl-4H-[1,2,4]triazole-3-thiol

A mixture of 2-methoxybenzhydrazide (7.0 gm, 42 mmol) and p-Tolyl isothiocyanate (6.3 gm, 42 mmol) in ethanol (100mL) was heated at reflux for one hour then cooled. The reaction mixture was filtered and the filter cake was washed with cold ethanol (50mL). The filter cake was dissolved in aqueous 2N sodium hydroxide (100mL) and heated overnight then cooled. The solution was neutralized with 6N hydrochloric acid and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a white solid. Trituration of the solid with ethanol (100mL) gave 5-(2-Methoxy-phenyl)-4-p-tolyl-4H-[1,2,4]triazole-3-thiol (11 gm, 37 mmol) as a white solid.

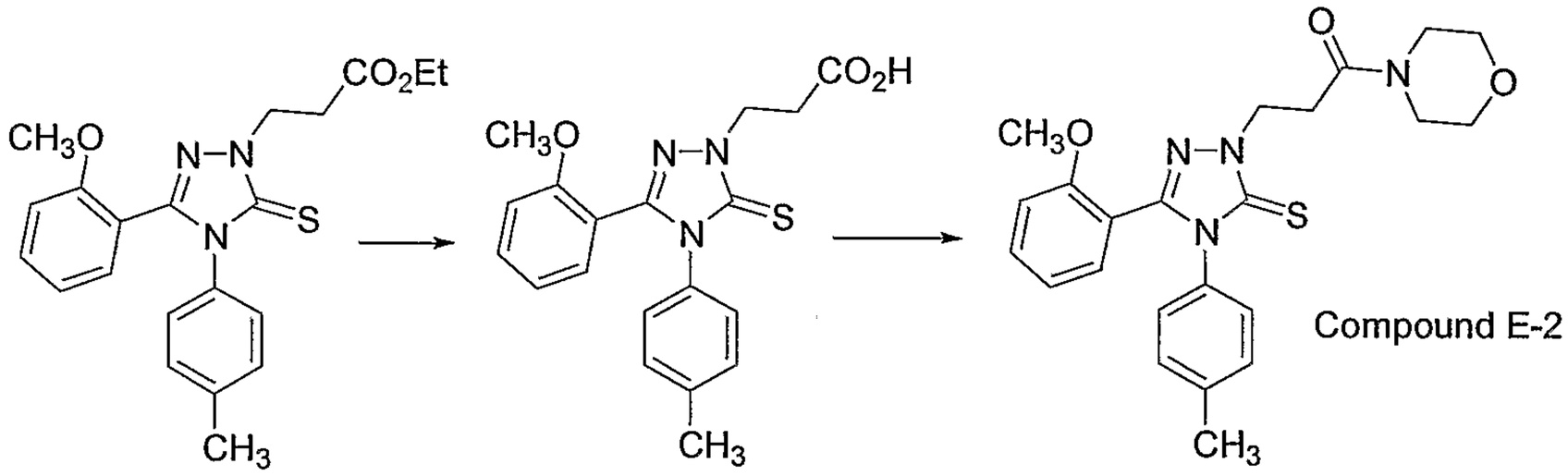
Part 2. Preparation of 3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid, ethyl ester

To a solution of 5-(2-methoxy-phenyl)-4-p-tolyl-4H-[1,2,4]triazole-3-thiol (0.9 g, 30.3 mmol) in DMF (100 mL) was added a 1M solution of lithium bis(trimethylsilyl)amide in THF (30.3 mL) and ethyl 3-bromopropionate (5.48 g, 30.3 mmol) at room temperature. The mixture was heated at 60°C for 1 hour and cooled to room temperature. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The residue was purified by chromatography on silica (20% ethyl acetate in n-hexane) to give 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid, ethyl ester (10.08 g, 25.4 mmol) as a clear oil.

Compound E-2

3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-1-morpholin-4-yl-propan-1-one

Scheme E-6



Part 1. Preparation of 3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid

A mixture of 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid, ethyl ester (10.08 g, 25.4 mmol) and lithium hydroxide hydrate (1.28 g, 30.48 mmol) was dissolved in 1,4-dioxane: water (4/1:v/v) and allowed to stir at room temperature for 3 hours. The reaction mixture was neutralized with aqueous 2N HCl and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid (8.99 g, 24.4 mmol) as a white solid.

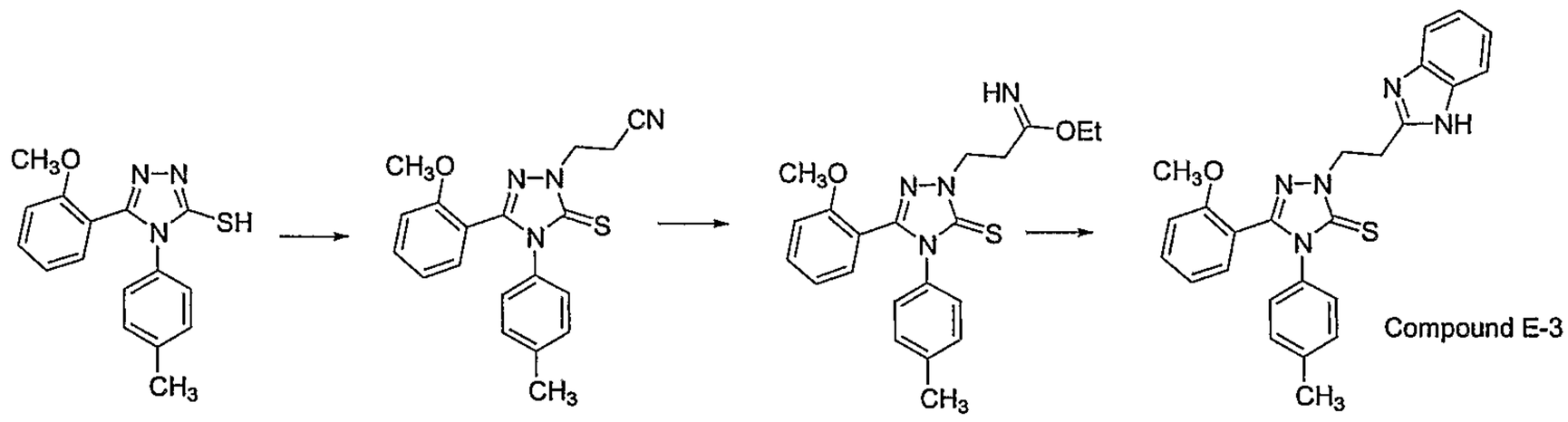
Part 2. Preparation of 3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-1-morpholin-4-yl-propan-1-one

To a solution of 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionic acid (0.50 g, 1.36 mmol , 1-3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.388 g, 2.03 mmol) and morpholine (0.177 g, 2.03 mmol) in THF (15 mL) was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The residue was purified by chromatography on silica (20% acetone in n-hexane) to give 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-1-morpholin-4-yl-propan-1-one (0.286 g, 0.65 mmol) as a white solid.

Compound E-3

2-[2-(1H-Benzoimidazol-2-yl)-ethyl]-5-(2-methoxy-phenyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

Scheme E-7



Part 1. Preparation of 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionitrile

A mixture of 5-(2-methoxy-phenyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (1.1 g, 3.7 mmol) in dioxane (6 mL) was stirred and Triton B (20 drops) was added. The mixture was heated to 70°C and acrylonitrile (250 μL, 3.7 mmol) was added and heated and additional 3 hours. The cooled mixture was partitioned

between aqueous 0.1N HCl (10 mL) and ethyl acetate (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and dried over sodium sulfate, filtered and the solvent removed under reduce pressure to give a viscous yellow oil. Flash chromatography (SiO_2, 2:3 ethyl acetate/hexane) gave 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionitrile (1 g, 2.8 mmol) as a white foam.

Part 2. Preparation of 3-[3-(2-Methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionimidic acid ethyl ester

A solution of propionitrile (0.5 g, 1.4 mmol) in 1:1 ethanol/diethylether (20 mL) was cooled in an ice water bath and HCl (g) was carefully bubbled in the solution over 10-20 minutes. The reaction mixture was stirred at room temperature for 2-4 hours and the solvent was removed under reduce pressure to obtain 3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propionimidic acid ethyl ester a viscous yellow oil. The oil used immediately without purification.

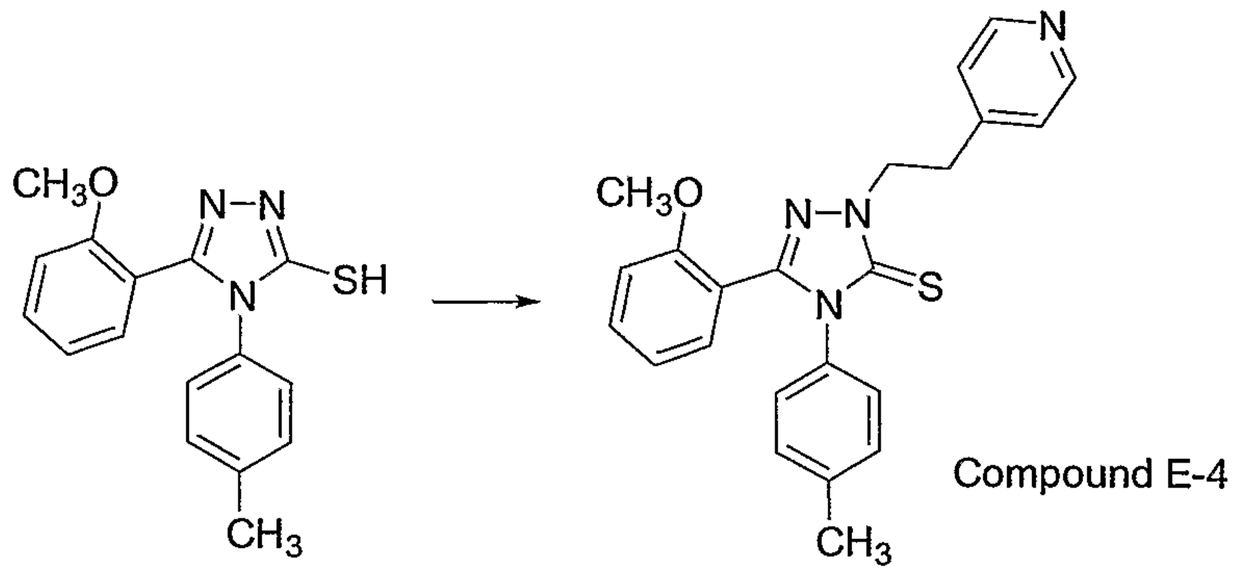
Part 3. Preparation of 2-[2-(1H-Benzoimidazol-2-yl)-ethyl]-5-(2-methoxy-phenyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

A mixture of the propionimidic acid ethyl ester and benzene-1,2-diamine (0.227 g, 2.1 mmol) in ethanol (10 mL) was stirred and heated at 60°C overnight. The solvent was removed under reduce pressure, the residue was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate, filtered, and the solvent removed under reduce pressure. Flash chromatography (SiO_2, 1:1 ethyl acetate/dichloromethane) gave a colorless oil. The oil was dissolved in methanol (2 mL) and treated with ethereal 2M HCl (10 mL). The solvent was removed under reduce pressure to provide the mono HCl salt of Compound E-3 (0.33 g) as a white solid.

<u>Compound E-4</u>

5-(2-Methoxy-phenyl)-2-(2-pyridin-4-yl-ethyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

Scheme E-8



Compound E-4

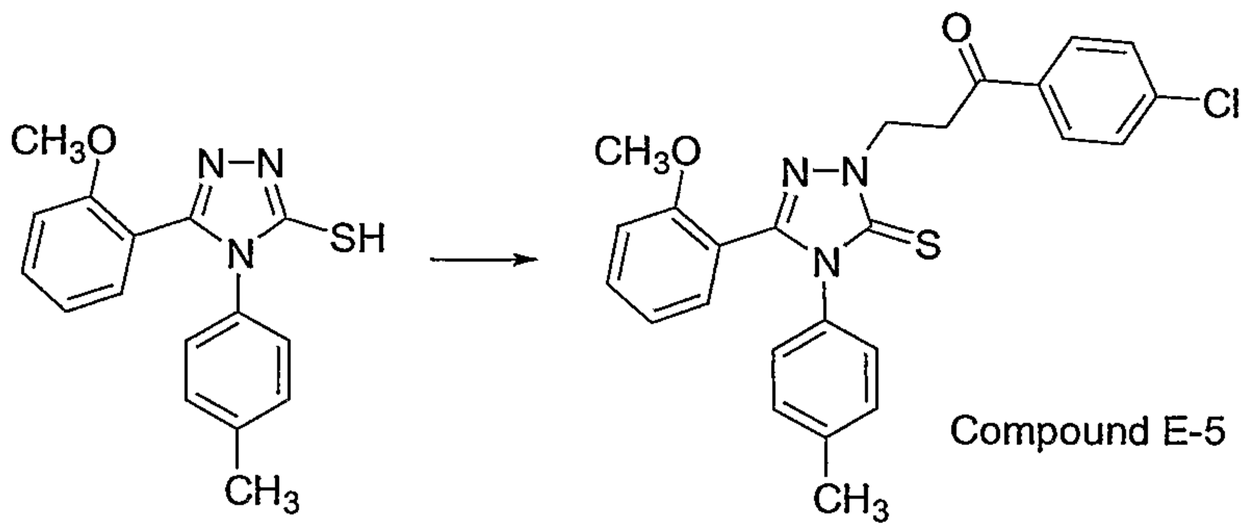
Part 1. Preparation of 5-(2-Methoxy-phenyl)-2-(2-pyridin-4-yl-ethyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione

A mixture of 5-(2-methoxy-phenyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.15 g, 0.50 mmol) in ethanol (10 mL) was stirred and 4-vinylpyridine (0.15 g, 1.0 mmol) was added. The mixture was heated overnight at refluxed then cooled. The cooled mixture was concentrated under vacuum and the residue diluted with ethyl acetate. The organics were washed with water (10 mL) and brine (10 mL) and dried over sodium sulfate, filtered and the solvent removed under reduce pressure to give a viscous yellow oil. Flash chromatography (SiO_2, 20% ethyl acetate/hexane) gave 5-(2-methoxy-phenyl)-2-(2-pyridin-4-yl-ethyl)-4-p-tolyl-2,4-dihydro-[1,2,4]triazole-3-thione (0.04 g, 0.09 mmol) as a white solid.

Compound E-5

1-(4-Chloro-phenyl)-3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propan-1-one

Scheme E-9



Compound E-5

Part 1. Preparation of 1-(4-Chloro-phenyl)-3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propan-1-one

To a solution of 5-(2-methoxy-phenyl)-4-p-tolyl-4H-[1,2,4]triazole-3-thiol (0.45 g, 1.5 mmol) in DMF (10 mL) was added a 1M solution of lithium bis(trimethylsilyl)amide in THF (1.5 mL) and beta-4-dichloropropiophenone (0.30 g, 1.5 mmol) at room temperature. The mixture was heated at 60°C for 1 hour and cooled to room temperature. The mixture was quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The residue was purified by chromatography on silica (20% ethyl acetate in n-hexane) to give 1-(4-chloro-phenyl)-3-[3-(2-methoxy-phenyl)-5-thioxo-4-p-tolyl-4,5-dihydro-[1,2,4]triazol-1-yl]-propan-1-one (0.19 g, 0.41 mmol) as a white solid.

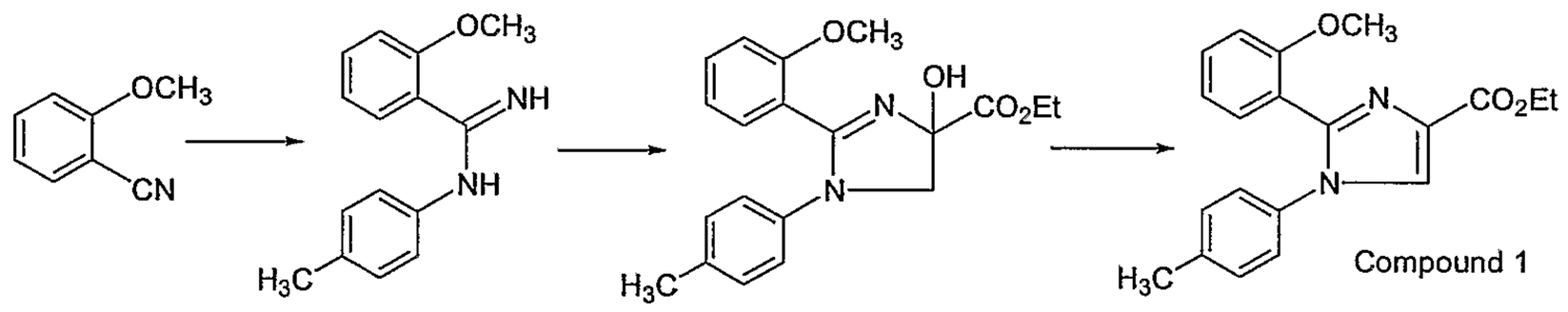
Example F-4

Compound F-1

2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester

(Compound 1 in Scheme F-5)

Scheme F-5



Part 1. Preparation of 2-Methoxy-*N*-*p*-tolyl-benzamidine

To a solution of sodium bis(trimethylsilyl)amide in THF (9.9 mL, 1M solution, 9.9 mmol) was slowly added at room temperature a solution of *p*-toluidine (1 g, 9.3 mmol) in dry THF (5 mL). After the mixture was stirred for 20 minutes, a solution of 2-methoxybenzonitrile (1.32 g, 9.9 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for 4 hours and quenched with water. The mixture was extracted with ethyl acetate three times. The combined organic layers were

washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 2-methoxy-*N*-*p*-tolyl-benzamidine as a red oil, which was used in the next step without further purification.

Part 2. Preparation of 4-Hydroxy-2-(2-methoxy-phenyl)-1-*p*-tolyl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid ethyl ester

A mixture of 2-methoxy-*N*-*p*-tolyl-benzamidine (340 mg, 1.5 mmol), $NaHCO_3$, (378 mg, 4.5 mmol) in THF/water (4/1: v/v, 10 mL) was heated at reflux. A solution of ethyl bromopyruvate (0.19 mL, 1.5 mmol) in THF (2 mL) was added over 5 minutes. The reaction mixture was refluxed for 2 hours, cooled to room temperature, extracted with ethyl acetate three times. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 4-hydroxy-2-(2-methoxy-phenyl)-1-*p*-tolyl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid ethyl ester as a brown solid and used without purification in the next step.

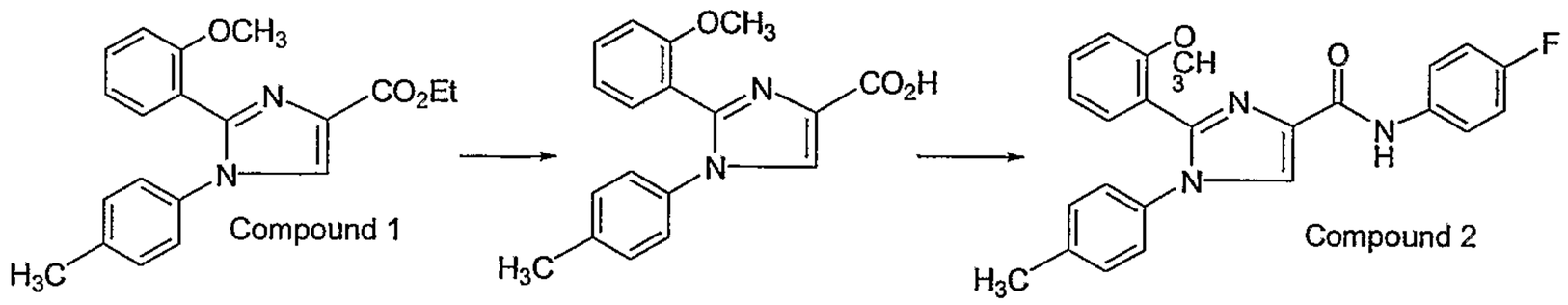
Part 3. Preparation of 2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester

To the flask of 4-hydroxy-2-(2-methoxy-phenyl)-1-*p*-tolyl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid ethyl ester (5 g, 14.1 mmol) in dry toluene (50 mL) was added *p*-toluenesulfonic acid (268 mg, 1.4 mmol). The resulting mixture was refluxed until starting material was consumed. The solvent was removed under vacuum and the resulting residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and chromatography on(SiO_2, 50% ethyl acetate in hexanes) provided 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester (4.5 g, 13.4 mmol) as a solid.

Compound F-2

2-(2-Methoxy-phenyl)-1-p-tolyl-1H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-methyl-amide (Compound 2 in scheme F-6)

Scheme F-6



Part 1. Preparation of 2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid

To a solution of 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester (4.5 g, 13.4 mmol) in methanol (10 mL) was added aqueous 2N NaOH (10 mL). The mixture was refluxed for 1 hour and cooled to room temperature. The solvents were partially removed under reduced pressure. The residue was acidified to pH 3, extracted with methylene chloride three times. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (4.1g, 13.4 mmol) as a solid.

Part 2. Preparation of 2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide

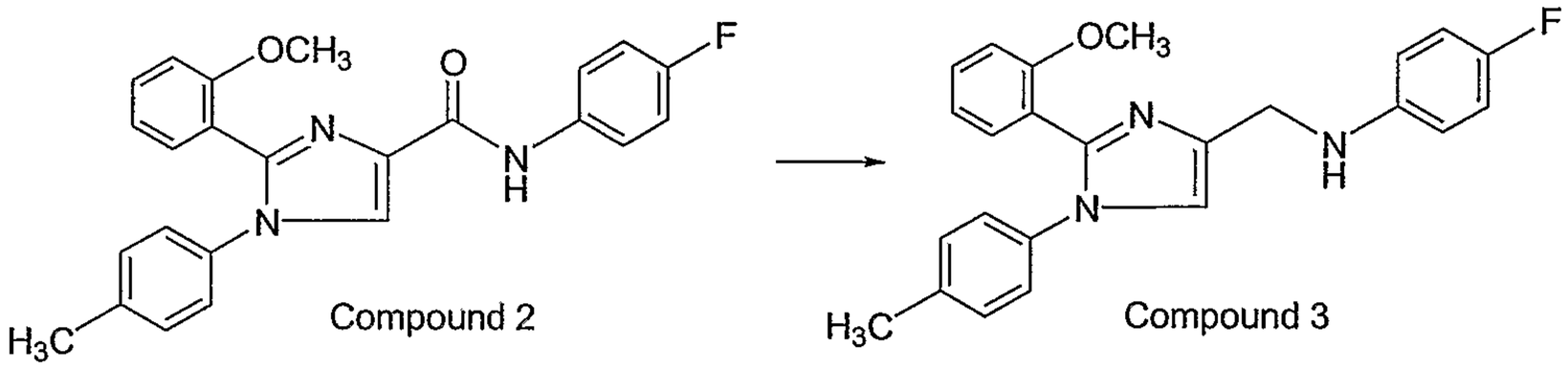
To the flask containing 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (740 mg, 2.4 mmol), 4-fluoroaniline (0.23 mL, 2.4 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (920 mg, 4.8 mmol) was added pyridine (10 mL). The mixture was stirred at room temperature for 1 hour and the volatile organics were removed. The residue was partitioned between methylene chloride and water. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Chromatography (SiO_2, 30% ethyl acetate in hexanes) afforded 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (900 mg, 2.2 mmol) as a solid.

Compound F-3

(4-Fluoro-phenyl)-[2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-ylmethyl]-amine

(Compound 3 in scheme F-7)

Scheme F-7

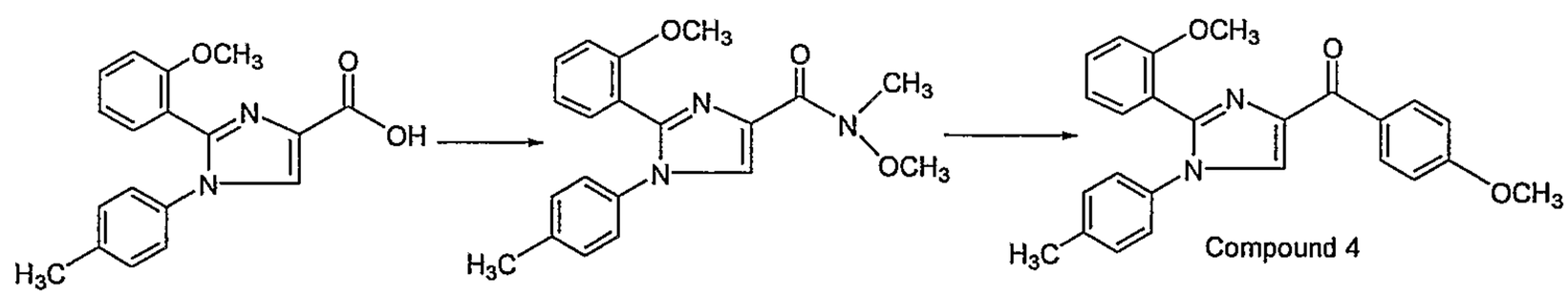


To a solution of 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (4-fluoro-phenyl)-amide (250 mg, 0.62 mmol) in toluene (6 mL) was added at room temperature borane dimethylsulfide complex THF solution (1.25 mL, 2M solution, 2.5 mL). The mixture was refluxed overnight. To the cooled reaction mixture was added aqueous 1N HCl. The mixture was refluxed for 30 minutes and cooled to room temperature. The solvents were partially removed under reduced pressure. The residue was neutralized with aqueous 1N NaOH and extracted with methylene chloride three times. The organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Chromatography (SiO_2, 30% ethyl acetate in hexanes) afforded (4-fluoro-phenyl)-[2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-ylmethyl]-amine (210mg, 0.54 mmol) as an oil.

Compound F-4

of 2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid methoxy-methyl-amide (Compound 4 in scheme F-8)

Scheme F-8



Part 1. Preparation of 2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid methoxy-methyl-amide

To a solution of 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid (200 mg, 0.65 mmol) in methylene chloride (5 mL) was added (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (250 mg, 1.3 mmol), triethylamine (0.18 mL, 1.3 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (63 mg, 0.65 mmol). The mixture was stirred overnight. The mixture was applied to partition between methylene chloride and saturated aqueous $NaHCO_3$. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Cohromatography (SiO_2, ethyl acetate) afforded 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid methoxy-methyl-amide (220 mg, 0.63 mmol) as an oil.

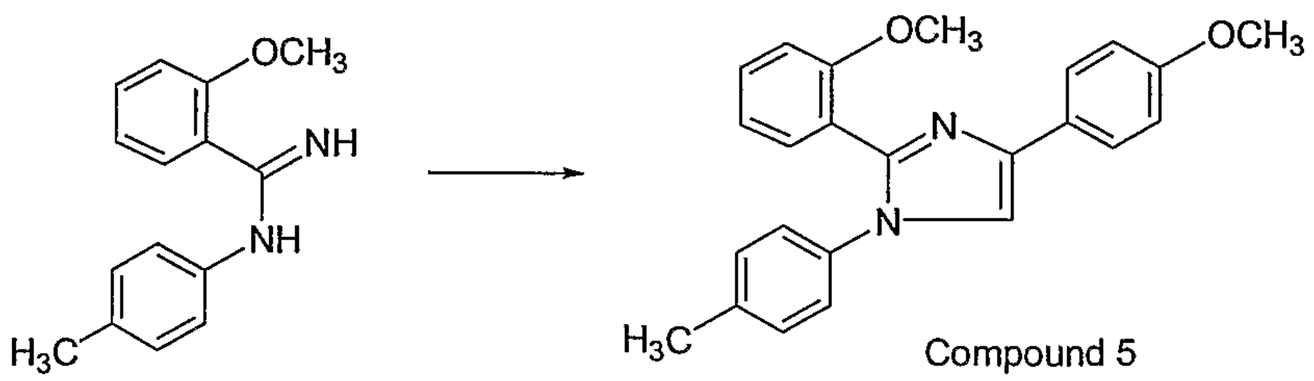
Part 2. Preparation of (4-Methoxy-phenyl)-[2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-yl]-methanone

To a solution of 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid methoxy-methyl-amide (110 mg, 0.31 mmol) in THF (2 mL) was slowly added 4-methoxyphenylmagnesium bromide THF solution (0.63 mL, 0.5 M solution, 0.31 mmol). The mixture was stirred overnight. Additional 0.5M 4-methoxyphenylmagnesium bromide in THF (0.63 mL, 0.31 mmol) was added and the mixture was stirred for 3 hours and quenched with water. The mixture was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Reversed phase liquid chromatography followed by plate chromatography (SiO_2, 50% ethyl acetate in hexanes) afforded (4-methoxy-phenyl)-[2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-yl]-methanone (9.1 mg, 0.04 mmol) as a foam.

Compound F-5

(4-Methoxy-phenyl)-2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole (Compound 5 in scheme F-9)

Scheme F-9



To a solution of 2-methoxy-*N*-*p*-tolyl-benzamidine (230 mg, 0.96 mmol) in acetonitrile (5 mL) was added $NaHCO_3$ (242 mg, 2.88 mmol). The mixture was heated to 50°C. A solution of 2-bromo-1-(4-methoxy-phenyl)-ethanone (220 mg, 0.96 mmol) in acetonitrile (2 mL) was added dropwise and the mixture was stirred at 50°C for 30 minutes and refluxed for 3 hours. The solvent was removed, the residue was applied to column chromatography (SiO_2, 30% ethyl acetate in hexane) to give (4-methoxy-phenyl)-2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole (320 mg, 0.86 mmol) as a solid.

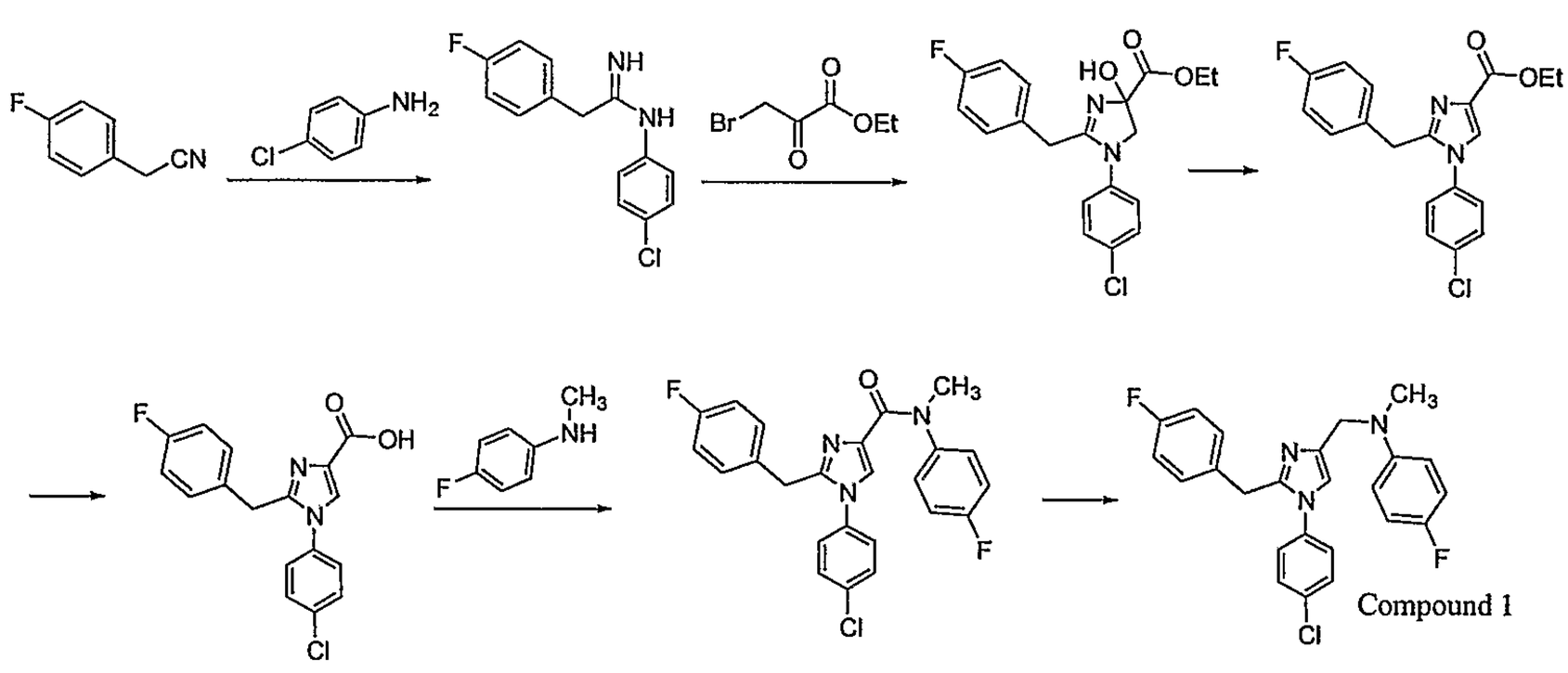
Example G-4

Representative compounds of the formulae herein were evaluated for activity against calcium channel targets.

Compound G-1

[1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-(4-fluoro-phenyl)-methyl-amine (Compound 1 in scheme G-6)

Scheme G-6



Part G-1. Preparation of N-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-acetamidine

To 4-chloroaniline (54.0 g, 424 mmol) in toluene (1000 mL) at 0 °C was added, dropwise, trimethylaluminum (2.0 *M* in toluene, 200 mL, 400 mmol) and the reaction warmed to room temperature over 3 hours under nitrogen. A solution of 4-fluorophenylacetonitrile (31.8 g, 235 mmol) in toluene (20 mL) was added and the mixture heated at 80 °C overnight. The mixture was cooled to room temperature, treated with chloroform (200 ml) and SiO_2, the slurry stirred 1 hour and poured onto a plug of SiO_2. Elution with 5:10:85 ammonium hydroxide:methanol:methylene chloride gave upon concentration *in vacuo* a light brown solid. Recrystallization from ethyl acetate/hexanes gave N-(4-chloro-phenyl)-2-(4-fluoro-phenyl)-acetamidine (54.5 g, 207 mmol) as a white solid.

Part G-2. Prepartion of 1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester

A solution of N-(4-chloro-phenyl)-2-(4-fluoro-phenyl)-acetamidine (6.2 g, 24 mmol), ethyl bromopyruvate (10.1 g, 52 mmol), and sodium hydrogen carbonate (8.9 g, 106 mmol) in THF (100 mL) and water (100 ml) was refluxed 4 hours. The mixture was cooled to room temperature and extracted with diethyl ether. The organics were dried and concentrated *in vacuo* to give a dark brown oil. Recrystallization from ethyl acetate/hexanes gave 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (1.8 g, 4.7 mmol) as a light brown solid.

Part G-3. Preparation of 1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid ethyl ester

A solution of 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (1.8 g, 4.7 mmol) and *p*-toluenesulfonic acid monohydrate (0.2 g, 0.9 mmol) in toluene (20 mL) was refluxed 2 hours. The mixture was cooled to room temperature, solvent removed *in vacuo*, and the residue partitioned between water and ethyl acetate. The organics were dried and concentrated *in vacuo* to give a dark red oil which was purified by chromatography

(SiO_2, 3% methanol in methylene chloride) to give 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid ethyl ester (1.6 g, 4.4 mmol).

Part G-4. Preparation of 1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid

To a solution of 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid ethyl ester (1.6 g, 4.4 mmol) in 1,4-dioxane (15 mL) and water (15 ml) was added lithium hydroxide hydrate (0.4 g, 8.7 mmol) and the mixture was stirred at 40 °C for 1 hour. Most 1,4-dioxane was removed *in vacuo*, the residue taken up in ethyl acetate/water, the aqueous washed with ethyl acetate, acidified to pH 2 with aqueous 2 *N* HCl and the precipitated 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid (1 g, 2.7 mmol) collected by filtration as a the white HCl salt.

Part G-5. Preparation of 1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-methyl-amide

A mixture of 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid (0.4 g, 1.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.3 g, 1.5 mmol) and 4-fluoro-N-methylaniline (0.2 g, 1.4 mmol) in methylene chloride (10 mL) was stirred at room temperature for 4 hours. Solvent was removed *in vacuo*, the residue taken up in water and extracted with ethyl acetate. The organics were dried, concentrated *in vacuo*, and the residue purified by chromatography (SiO_2, 3% methanol in methylene chloride) to give 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-methyl-amide (0.4 g, 0.9 mmol).

Part G-6. Preparation of [1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-(4-fluoro-phenyl)-methyl-amine

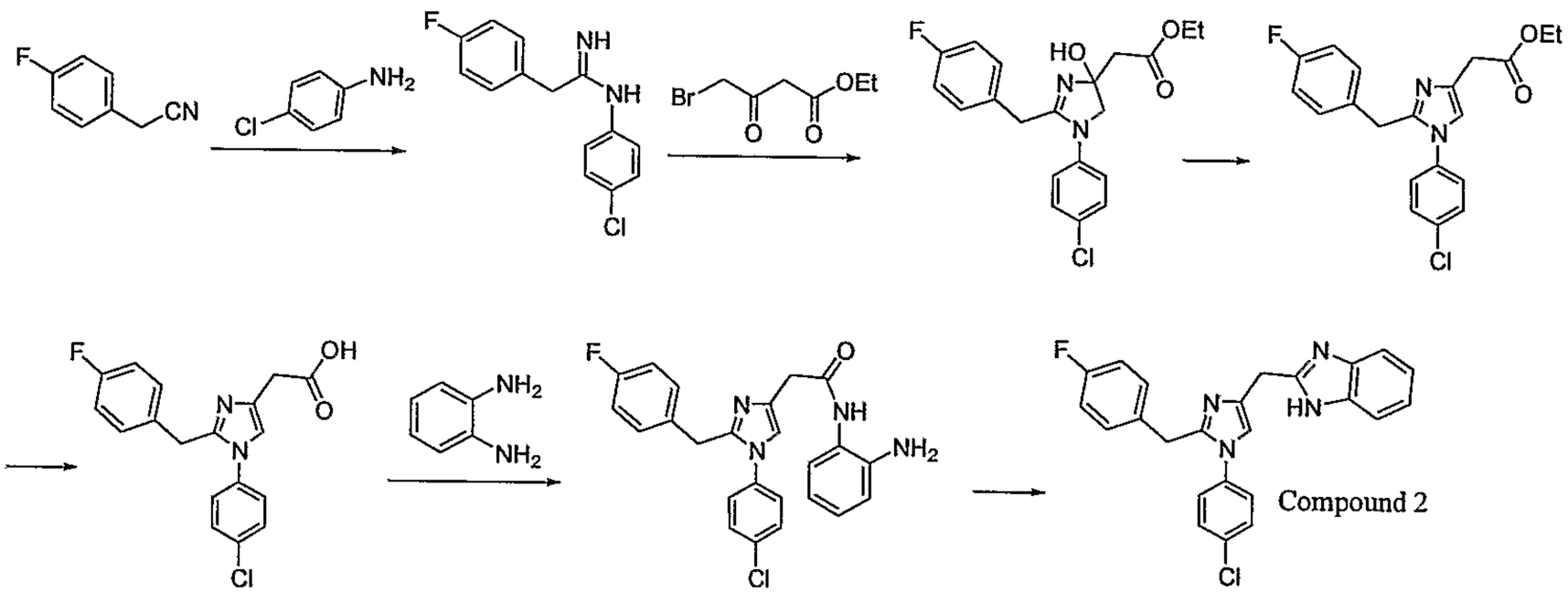
To a solution 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazole-4-carboxylic acid (4-fluoro-phenyl)-methyl-amide (0.3 gm, 0.7mmol) in THF (10 mL) at 0 °C was added borane-dimethylsufide complex (2M in THF, 1.0mL, 2.0 mmol) and the reaction heated at reflux overnight. The mixture was cooled and diluted with methanolic HCl (10 mL), heated at reflux for 1 hour ,cooled, and concentrated *in*

vacuo. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give an oil. Purification by chromatography (SiO_2, 3% methanol in methylene chloride) gave an oil which was taken up in ethanol and treated with HCl in ether to give 1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-(4-fluoro-phenyl)-methyl-amine (0.1 g, 0.2 mmol) as the off-white HCl salt.

Compound G-2

2-[1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole (Compound 2 in scheme G-7)

Scheme G-7



Parts G-1-5. Preparation of N-(2-Amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-yl]-acetamide

N-(2-Amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-yl]-acetamide was made as in Scheme 6 substituting ethyl 4-bromoacetoacetate for ethyl bromopyruvate in Part 2 and 1,2-phenylenediamine for 4-fluoro-N-methylaniline in Part G-5.

Part G-6. Preparation of 2-[1-(4-Chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole

A solution of N-(2-amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-yl]-acetamide (3.8 g, 8.7 mmol) in glacial acetic acid (10 mL) was heated at 70 °C for 0.5 hours. The mixture was cooled, added dropwise to saturated aqueous sodium hydrogen carbonate, the pH adjusted to ~14 with sodium hydroxide, extracted with ethyl acetate, and the organics dried and concentrated *in vacuo* to give an oil. Treatment with HCl in ether followed by recrystallization from methanol/ether gave 2-[1-(4-chloro-phenyl)-2-(4-fluoro-benzyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole (2.0 g, 4.8 mmol) as the white HCl salt.

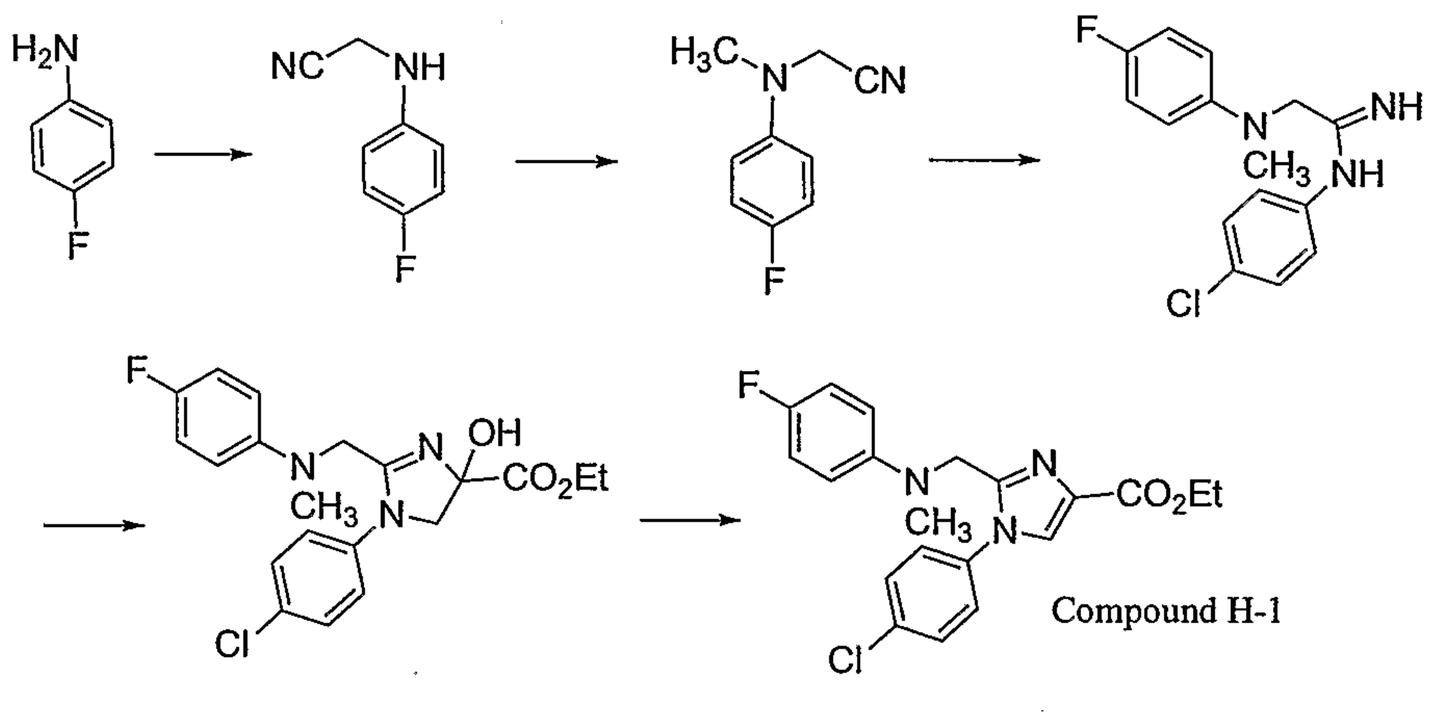
Example H-4

Representative compounds of the formulae herein are evaluated for activity against calcium channel targets

Compound H-1

1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid ethyl ester

Scheme H-6



Part H-1. Preparation of (4-Fluoro-phenylamino)-acetonitrile

To a solution of 4-fluoroaniline (20.0 g, 180 mmol) in glacial acetic acid (250 mL) was added portion wise paraformaldehyde (14.06 g) and potassium cyanide (14.06 g, 216 mmol) at 0°C. The mixture was allowed to stir at room temperature overnight

and cooled. The mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The resulting residue was purified by chromatography (SiO_2, 10% ethyl acetate in n-hexane to give (4-fluoro-phenylamino)-acetonitrile (22.9 g, 153 mmol) as a yellow oil.

Part H-2. Prepartion of [(4-Fluoro-phenyl)-methyl-amino]-acetonitrile

To a slurry of (4-fluoro-phenylamino)-acetonitrile (22.9 g, 153 mmol) and cesium carbonate (74.8 g, 229 mmol) in THF (200 mL) was added iodomethane (10.5 mL, 168mmol). The mixture was stirred for 3 hours at 40°C, cooled and quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give [(4-fluoro-phenyl)-methyl-amino]-acetonitrile (22.3 g, 136 mmol) as an oil.

Part H-3. Preparation of N-(4-Chloro-phenyl)-2-[(4-fluoro-phenyl)-methyl-amino]-acetamidine

To a solution of 4-chloroaniline (1.4 g, 11.0 mmol) in toluene (50 mL) was added trimethylaluminum (2M in toluene; 5.3 mL, 10.4 mmol) at 0 °C under a nitrogen blanket. The slurry was allowed to stir for 1 hour and added to a solution of [(4-fluoro-phenyl)-methyl-amino]-acetonitrile (1.0 g, 6.2 mmol) at room temperature. The mixture was heated at 80°C overnight, cooled and quenched with a slurry of silica/chloroform mixture. The resulting mixture was filtered over a short bed of silica and washed with 10% methanol in methylene chloride. The combined fractions gave N-(4-chloro-phenyl)-2-[(4-fluoro-phenyl)-methyl-amino]-acetamidine (1.21 g, 4.18 mmol) as yellow oil.

Part H-4. Preparation of 1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester

To a solution of N-(4-chloro-phenyl)-2-[(4-fluoro-phenyl)-methyl-amino]-acetamidine (1.21 g, 4.18 mmol) in THF (40 mL) was added sodium bicarbonate (0.70 g, 8.36 mmol) in water (10 mL) followed by slow addition of ethyl

bromopyruvate (1.22 gm, 6.27 mmol) at 40°C. After addition, the reaction was heated at 40°C for 2 hours and cooled. The mixture was diluted with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The resulting residue was purified by chromatography (SiO_2, 30% ethyl acetate in n-hexane) to give 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (0.74 g, 1.84 mmol) as a dark oil.

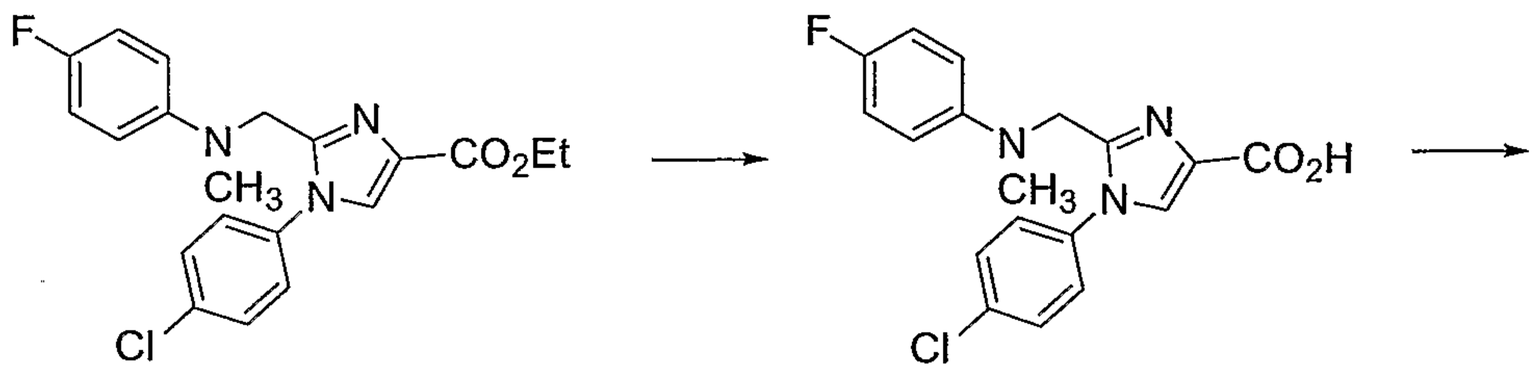
Part H-5. Preparation of 1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid ethyl ester

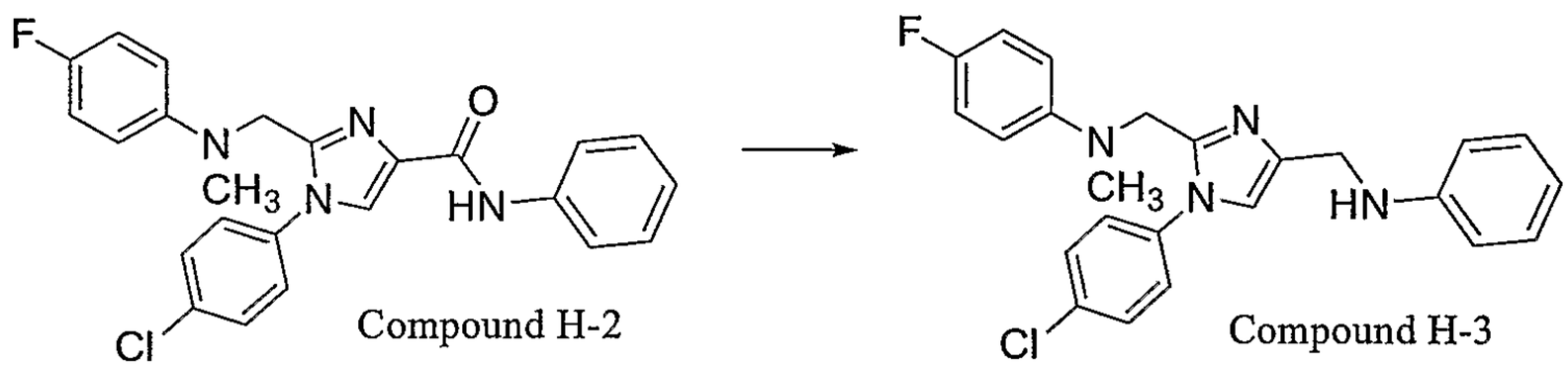
A mixture of 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (0.74 gm, 1.84 mmol) and p-toluenesulfonic acid monohydrate (0.1 gm) in toluene (20 mL) was heated at reflux for 1 hour. The mixture was cooled, quenched with water and extracted with ethyl acetate. The organics were dried and concentrated under vacuum. The resulting residue was purified by chromatography (SiO_2, 15% acetone in n-hexane) to give 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid ethyl ester (0.63 g, 1.62 mmol) as a white solid.

Compound H-2 and H-3

1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid phenylamide and [1-(4-Chloro-phenyl)-4-phenylaminomethyl-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine

Scheme H-7





Part H-1. Preparation of 1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid

A solution of 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid ethyl ester (0.63 g, 1.62 mmol) and lithium hydroxide hydrate (0.14 g, 3.24 mmol) in a methanol/ water mixture (2:1/ v:v) was heated at 50°C for 1 hour and cooled. The reaction mixture was concentrated under vacuum and diluted with aqueous 6N HCl until a pH of 6.5 was attained. The aqueous layer was extracted with ethyl acetate and the organics were dried, concentrated under vacuum to give 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid (0.41 g, 1.15 mmol) as a white solid.

Part H-2. Preparation of1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid phenylamide

A mixture of 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid (0.36 g, 1.00 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.28 g, 1.5 mmol) and aniline (0.09 g, 1 mmol) in pyridine (4 mL) was heated at 40 °C overnight. The mixture was cooled, quenched with water and extracted with ethyl acetate. The organics were dried, concentrated under vacuum to 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid phenylamide (0.31 g, 0.71mmol) as a solid.

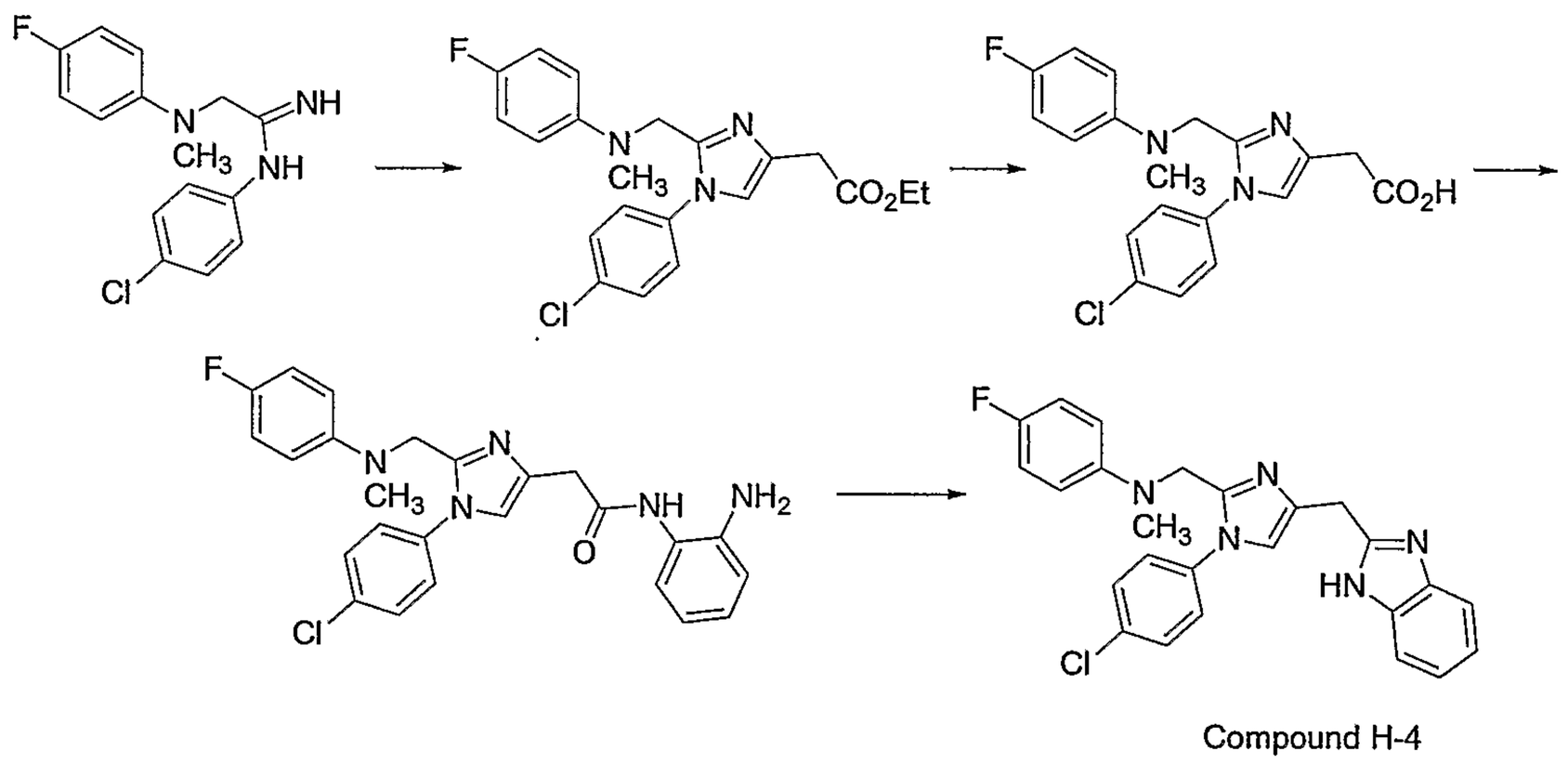
Part H-3. Preparation of [1-(4-Chloro-phenyl)-4-phenylaminomethyl-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine

To a solution 1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazole-4-carboxylic acid phenylamide (0.26 g, 0.6mmol) in THF (15 mL) was added borane-dimethylsufide complex (2M in THF; 0.9mL) and allowed to stir overnight at reflux. The mixture was cooled and diluted with methanolic HCl (10 mL). The mixture was heated again at reflux for 1 hour, cooled and concentrated under vacuum to give a residue. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were dried and concentrated under vacuum to give a solid. Purification by chromatography (SiO_2, 40% acetone in n-hexane) gave [1-(4-chloro-phenyl)-4-phenylaminomethyl-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine (0.07 g, 0.17 mmol) as a white solid.

Compound H-4

[4-(1H-Benzoimidazol-2-ylmethyl)-1-(4-chloro-phenyl)-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine

Scheme H-8



Compound H-4

Part H-1. Preparation of (1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazol-4-yl)-acetic acid ethyl ester

[1-(4-chloro-phenyl)-4-phenylaminomethyl-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine (1 eq.) and potassium hydrogencarbonate (3 eq) is suspended in acetonitrile. The suspension is heated to 50°C and 4-bromo-3-oxo-butyric acid ethyl ester (1.5 eq.) in acetonitrile is added slowly dropwise . The reaction mixture is refluxed for 2 hours and cooled. The resulting residue is purified by chromatography (SiO_2, ethyl acetate in hexane to give [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid ethyl ester.

Part H-2. Preparation of (1-(4-Chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazol-4-yl)-acetic acid

To a solution of (1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazol-4-yl)-acetic acid ethyl ester (1 eq.) in THF is added 1N aqueous sodium hydroxide (5 eq). The mixture is stirred for 1 hour at 70°C and cooled. The reaction is diluted with water and the aqueous layer the pH is adjusted to 6 using 6N aqueous sodium hydroxide. The aqueous phase is extracted with ethyl acetate, washed with water, dried and concentrated under vacuum to give (1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazol-4-yl)-acetic acid.

Part H-3. Preparation of N-(2-Amino-phenyl)-2-(1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-ethyl-amino]-methyl}-1H-imidazol-4-yl)-acetamide

A mixture of (1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-methyl-amino]-methyl}-1H-imidazol-4-yl)-acetic acid (1 eq.) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2 eq) and 1,2-phenylenediamine (1 eq.) in pyridine is stirred at room temperature overnight. The solvent is removed under vacuum, the resulting residue is diluted with water and extracted with ethyl acetate. The organics will be dried, concentrated and the residue is purified by chromatography on silica gel (methanol in methylene chloride) to give N-(2-amino-phenyl)-2-(1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-ethyl-amino]-methyl}-1H-imidazol-4-yl)-acetamide.

Part H-4. Preparation of [4-(1H-Benzoimidazol-2-ylmethyl)-1-(4-chloro-phenyl)-1H-imidazol-2-ylmethyl]-(4-fluoro-phenyl)-methyl-amine

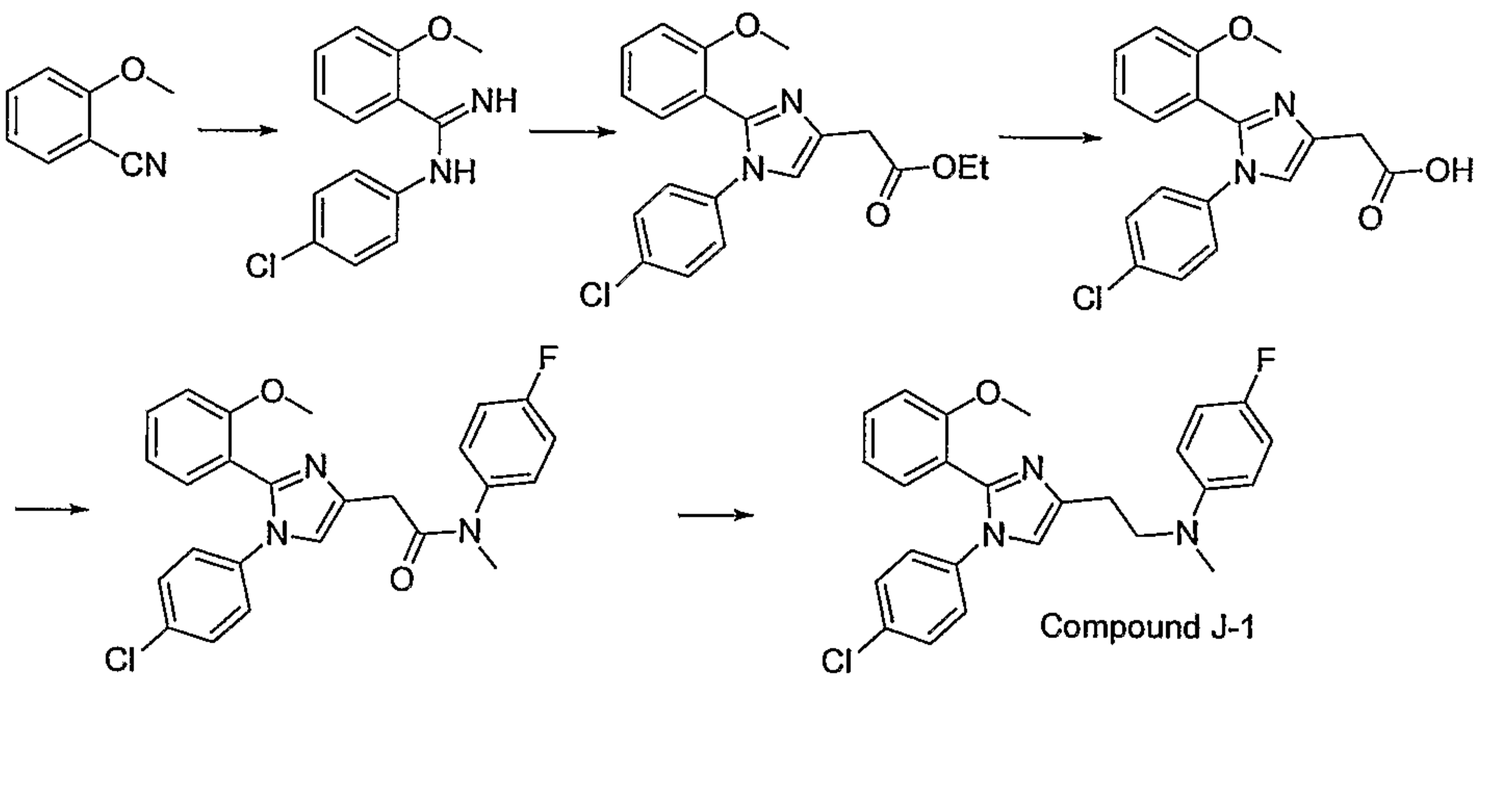
A solution of N-(2-amino-phenyl)-2-(1-(4-chloro-phenyl)-2-{[(4-fluoro-phenyl)-ethyl-amino]-methyl}-1H-imidazol-4-yl)-acetamide (1 eq.) in glacial acetic acid is to be heated at 70°C for 30 minutes. The mixture is cooled and saturated aqueous sodium bicarbonate solution is added. The pH is adjusted to 7 with sodium hydroxide pellets and the aqueous layer extracted with ethyl acetate. The organics are dried and concentrated under vacuum to give a residue. The residue is treated with HCl in ether to give 2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole (0.44 gm, 0.98 mmol) as an HCl salt.

Example J-4

Compound 1

[1-(4- {2-[1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-ethyl}-(4-fluoro-phenyl)-methyl-amine

Scheme J-6



Part J-1. Preparation of N-(4-Chloro-phenyl)-2-methoxy-benzamidine

To a solution of 4-chloroaniline (25 g, 197 mmol) in THF (250 mL) at 0°C was added in a dropwise fashion a 1M solution of sodium bis(trimethylsilyl)amide in THF

(207 mL, 1.06eq) over a period of 30 to 60 minutes. After the addition was complete, a solution of 2-methoxy benzonitrile (27.6 g, 209 mmol) in THF (125 mL) was added dropwise over a period of 15 to 30 minutes at room temperature and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered and the solvent was removed under reduce pressure to give dark oil that solidified upon standing. Titration with hexane and a minimal amount of ethyl acetate gave after filtration N-(4-chloro-phenyl)-2-methoxy-benzamidine (34 g, 131 mmol) as a grey solid.

Part J-2. Preparation of [1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid ethyl ester

A 50 °C mixture of N-(4-chloro-phenyl)-2-methoxy-benzamidine (9 g, 34.6 mmol) and potassium hydrogencarbonate (10.38 g, 103.8 mmol, 3 eq) in acetonitrile (100 mL) was treated with a solution of 4-bromo-3-oxo-butyric acid ethyl ester (10 g, 48 mmol) in acetonitrile (50 mL) dropwise over 30 minutes. The reaction mixture was brought to reflux for 2 hours, cooled and filtered. Under vacuum the solvent was removed from the filtrate to give a dark oil. Flash chromatography (SiO_2, 50% ethyl acetate in hexane) gave [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid ethyl ester (16 g, 17 mmol) as a dark, viscous oil.

Part J-3. Preparation of [1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid

To a solution of [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid ethyl ester (1.5 g, 4.04 mmol) in THF (40 mL) was added aqueous 1N sodium hydroxide (12 mL) and the mixture allowed to stir for 1 hour at 70°C and cooled. The reaction was quenched with water and adjusted to pH 6 with aqueous 6N sodium hydroxide and extracted with ethyl acetate. The combined organics were washed with water, dried and concentrated under vacuum to give [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid (0.49 g, 1.43 mmol) as a white solid.

Part J-4. Preparation of 2-[1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-N-(4-fluoro-phenyl)-N-methyl-acetamide

A mixture of [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid (0.25 g, 0.73 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.28 g, 1.46 mmol) and 4-fluoro-N-methylaniline (0.082 mL, 0.73 mmol) in pyridine (3 mL) was stirred at room temperature overnight. The solvent was removed in vacuo, the residue diluted with water and extracted with ethyl acetate. The organics were dried, concentrated under reduced pressure and the residue purified by chromatography (SiO_2, 3% methanol in methylene chloride) to give 2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-N-(4-fluoro-phenyl)-N-methyl-acetamide (0.16 g, 0.36 mmol) as an oil.

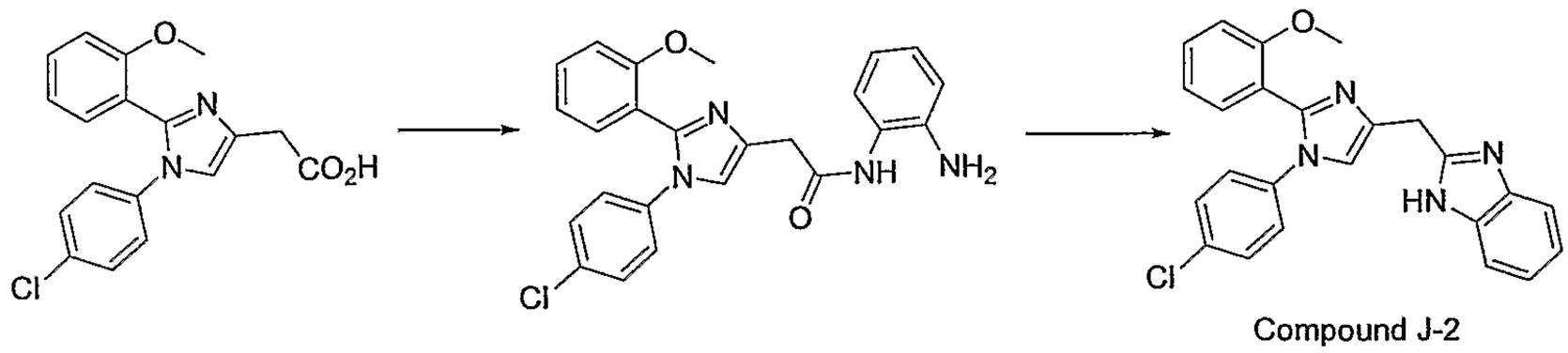
Part J-5. Preparation of [1-(4- {2-[1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-ethyl}-(4-fluoro-phenyl)-methyl-amine

To a solution of 2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-N-(4-fluoro-phenyl)-N-methyl-acetamide (0.07 g, 0.16 mmol) in toluene (5 mL) at 0°C was added borane-dimethylsulfide complex (2M in THF, 0.16 mL, 0.31mmol) and the reaction heated at reflux overnight. The mixture was cooled and diluted with methanolic HCl (3 mL), heated at reflux for 1 hour, cooled and concentrated under vacuum. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were dried, and concentrated under vacuum to give a white solid. The solid was taken up in methanol and treated with HCl in ether to give [1-(4- {2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-ethyl}-(4-fluoro-phenyl)-methyl-amine (0.06 g, 0.013 mmol) as a white solid.

Compound J-2

2-[1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole

Scheme J-7



Compound J-2

Part J-1. Preparation of N-(2-Amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetamide

A mixture of [1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetic acid (0.87 g, 2.56 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.73 g, 3.83mmol) and 1,2-phenylenediamine (0.28 g, 2.56 mmol) in pyridine (5 mL) was stirred at room temperature overnight. The solvent was removed in vacuo and was treated with water and made basic with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organics were dried and concentrated to give N-(2-amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetamide (0.86 g, 1.99 mmol) as an oil.

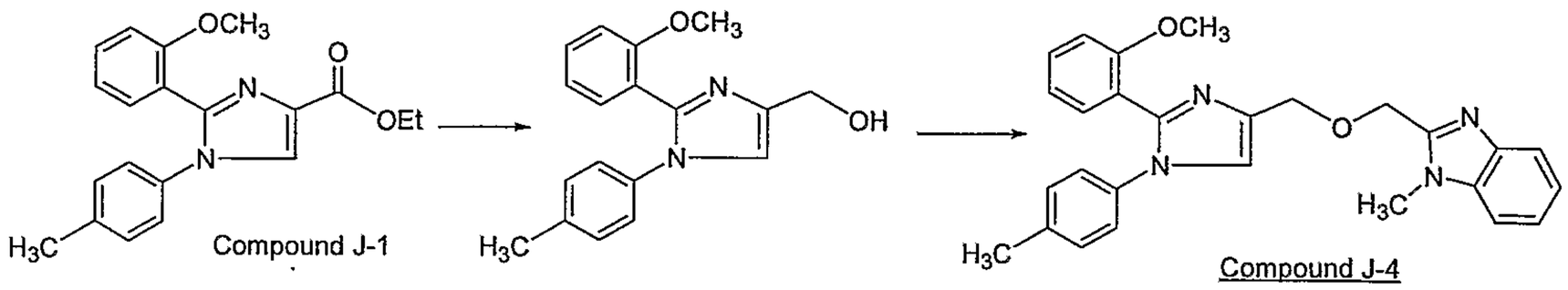
Part J-2. Preparation of 2-[1-(4-Chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole

A solution of N-(2-amino-phenyl)-2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-yl]-acetamide (0.86 g, 1.99 mmol) in glacial acetic acid (8 mL) was heated at 70°C for 30 minutes. The mixture was cooled and added dropwise to a saturated aqueous sodium bicarbonate and the pH adjusted to 7 with sodium hydroxide pellets. The mixture was extracted with ethyl acetate, the organics dried and concentrated in vacuum to give an oil. Treatment of the oil with HCl in ether gave 2-[1-(4-chloro-phenyl)-2-(2-methoxy-phenyl)-1H-imidazol-4-ylmethyl]-1H-benzoimidazole (0.44 g, 0.98 mmol) as a white solid.

Compound J-3

2-[2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-ylmethoxymethyl]-1-methyl-1*H*-benzoimidazole

Scheme J-8



Part J-1. Preparation of [2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-yl]-methanol

To a -78°C solution of 2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester (2.0 g, 6.0 mmol) in THF (10 mL) was added dropwise 1M lithium aluminum hydride in ether (6.0 mL, 6.0 mmol). The mixture was warmed to room temperature, stirred for 4 hours and quenched with three drops of methanol. The solvents were removed. The residue was partitioned between methylene chloride and water. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography (SiO_2, ethyl acetate) afforded [2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-yl]-methanol (1.1 g, 3.7 mmol) as a solid.

Part J-2. Preparation of 2-[2-(2-Methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-ylmethoxymethyl]-1-methyl-1*H*-benzoimidazole

To a solution of [2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-yl]-methanol (100 mg, 0.34 mmol) in THF (5 mL) was added NaH (15 mg, 0.34 mmol). The mixture was stirred at room temperature for 30 minutes and 2-chloromethyl-1-methyl-1*H*-benzoimidazole (61 mg, 0.34 mmol) was added. The mixture was refluxed for 1 hour, cooled to room temperature and quenched with water. The mixture was extracted with ether. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography (SiO_2, ethyl acetate) afforded 2-[2-(2-methoxy-phenyl)-1-*p*-tolyl-1*H*-imidazole-4-ylmethoxymethyl]-1-methyl-1*H*-benzoimidazole (86 mg, 0.20 mmol) as an oil.

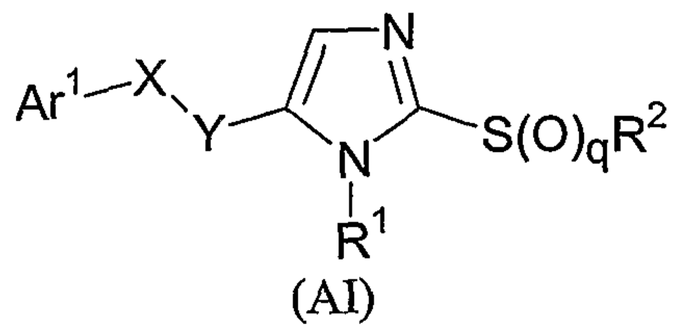
Compounds in the tables herein are prepared in a manner similar as described above and in the general schemes.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula (AI) or pharmaceutical salt thereof



(AI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3, $C(R^3)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0, 1 or 2;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

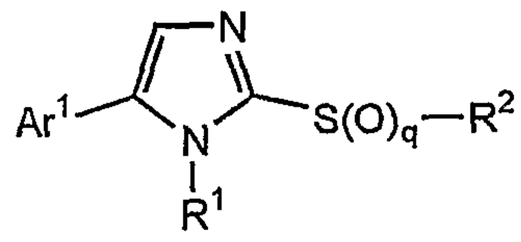
each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

2. A compound of formula (BI) or pharmaceutical salt thereof



BI

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group

consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

q is 0, 1 or 2;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$ or $(CH_2)_nOR^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, with the proviso that Ar^3 is not piperidinyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl;

each Z is independently selected from O or NR^3;

each m is 1 or 2;

each n is 2 or 3;

each p is 0 or 1;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

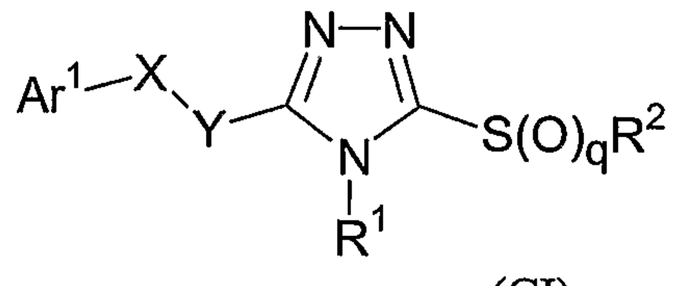
each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

3. A method of treating a disease or disease symptom in a subject comprising administering to the subject an effective amount a compound of formula CI or pharmaceutical salt thereof:



(CI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^3, $C(R^3)_2$, S, a bond or O, or together with Y forms -CH=CH-;

Y is C=O, a bond, or lower alkyl, or together with X forms -CH=CH-;

R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0,1 or 2;

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_3Ar^3$, $(CH_2)_nNR^3R^4$, $(CH_2)_nOR^4$; $(CH_2)_mCN$; alkyl; alkynyl, $(CR^3R^3)_mCONR^3R^4$, Ar^4, $(CR^3R^3)_mN(R^3)C(O)Ar^3$, or $(CH_2)_mC(NOH)NH_2$;

each R^3 is independently H, or lower alkyl;

each R^4 is independently H, lower alkyl, alkoxy, $(CH_2)_n NR^5R^6$, or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

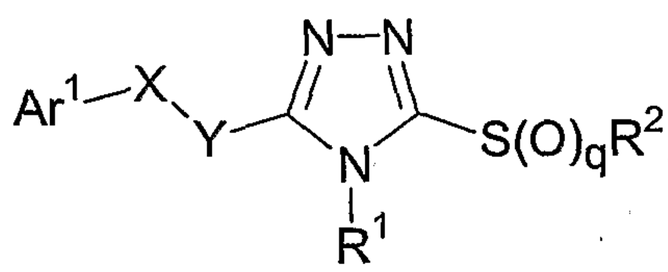
each R^5 is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently C_3-C_6 cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

4. A compound of formula CI or pharmaceutical salt thereof,



(CI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents, and each attached to X by a carbon atom;

X is CH_2;

Y is a bond;

R^1 is Ar^2 , alkenyl, or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

q is 0,1 or 2;

each R^2 is independently $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, or $(CH_2)_mCONR^3R^4$;

each R^3 is independently H, or lower alkyl;

each R^4 is independently H, lower alkyl, alkoxy, $(CH_2)_n NR^5R^6$, or $(CH_2)_pAr^3$;

m is 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^6)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^5C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

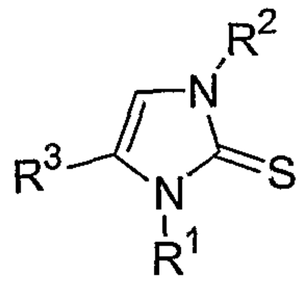
each R^5 is independently hydrogen or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently C_3-C_6 cycloalkyl, heterocyclyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

5. A compound of formula (DI) or pharmaceutical salt thereof



(DI)

wherein,

R^3 is Ar^1 or Ar^1-X-Y wherein,

each Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^4, $C(R^4)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is independently selected from $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$, $(CH_2)_mC(O)NR^4R^5$, $(CH_2)_nNR^4R^5$, $(CH_2)_3Ar^3$, or $(CH_2)_mAr^3$;

each R^4 is independently selected from H, or lower alkyl;

each R^5 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^6$, NR^6R^7, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^6$, $C(O)NR^6R^7$,

$OC(O)NR^6R^7$, $NR^6C(O)NR^6R^7$, $C(NR^6)NR^6R^7$, $NR^6C(NR^7)NR^6R^7$, $S(O)_2NR^6R^7$, R^8, $C(O)R^8$, $NR^6C(O)R^8$, $S(O)R^8$, or $S(O)_2R^8$;

each R^6 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

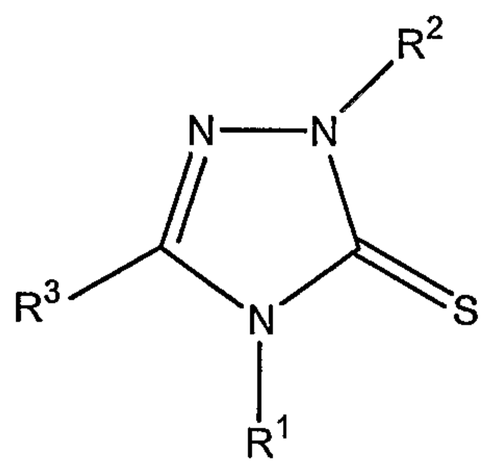
each R^7 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^8 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

q is 0 or 1.

6. A compound of formula (EI) or pharmaceutical salt thereof



(EI)

wherein,

R^3 is alkyl, alkoxyalkyl, Ar^1 or Ar^1-X-Y wherein,

each Ar^1 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

X is NR^4, $C(R^4)_2$, or O;

Y is C=O or lower alkyl;

R^1 is H, alkenyl, Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each R^2 is independently selected from H, $(CH_2)_mC(O)OR^4$, $(CH_2)_mC(O)Ar^3$, $(CH_2)_mC(O)NR^4R^5$, $(CH_2)_mC(O)N(OR^4)R^5$, $(CH_2)_mCH_2OR^4$, Ar^3, $(CH_2)_nNR^4R^5$, or $(CH_2)_mAr^3$;

each R^4 is independently selected from H, or lower alkyl;

each R^5 is independently selected from H, lower alkyl or $(CH_2)_pAr^3$;

m is 1 or 2;

n is 2 or 3;

p is 0 or 1;

each Ar^3 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each substituent for Ar^1, Ar^2 and Ar^3 is independently selected from halogen, CN, NO_2, OR^6, SR^6, $S(O)_2OR^6$, NR^6R^7, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^6$, $C(O)NR^6R^7$, $OC(O)NR^6R^7$, $NR^6C(O)NR^6R^7$, $C(NR^6)NR^6R^7$, $NR^6C(NR^7)NR^6R^7$, $S(O)_2NR^6R^7$, R^8, $C(O)R^8$, $NR^6C(O)R^8$, $S(O)R^8$, or $S(O)_2R^8$;

each R^6 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

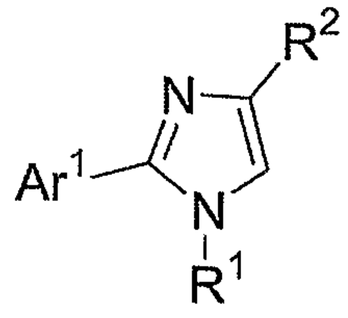
each R^7 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^8 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

q is 0 or 1.

7. A method for treating a disease or disease symptom in a subject comprising administering to the subject an effective amount of a compound of formula (FI) or pharmaceutical salt thereof:



(FI)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, Ar^3, $CH_2NR^3R^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

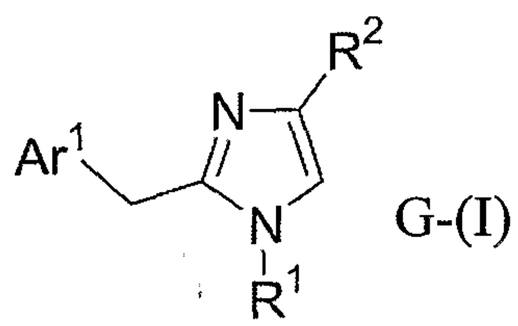
each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen,

OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

8. A compound of formula G- (I) or pharmaceutical salt thereof



G-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_nNR^3R^4$ or CH_2OR^4;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each n is independently 1 or 2;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

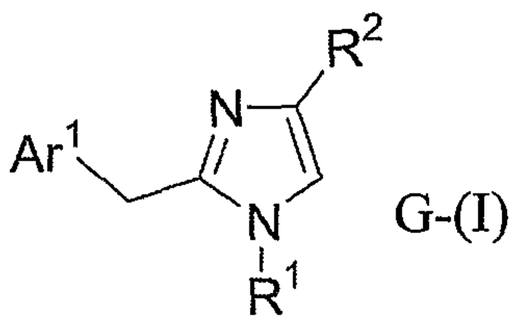
each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

9. A method for treating a disease or disease symptom in a subject in need of such treatment comprising administering an effective amount of a compound of formula G-(I) or pharmaceutical salt thereof:



G-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $(CH_2)_nNR^3R^4$ or CH_2OR^4;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each n is independently 1 or 2;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

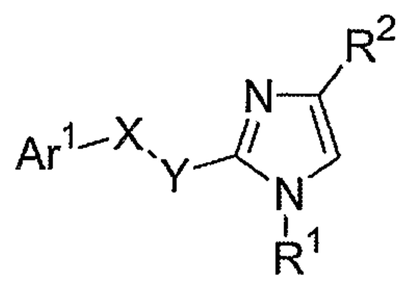
each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

10. A compound of formula H- (I) or pharmaceutical salt thereof



H-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

X is NR^3, $C(R^3)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $CH_2NR^3R^4$ or CH_2OR^4;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

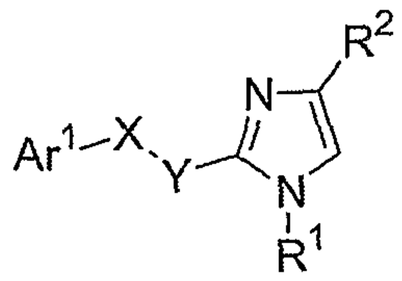
each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

11. A method for treating a disease or disease symptom in a subject in need of such treatment comprising administering to the subject an effective amount of a compound of formula H- (I) or pharmaceutical salt thereof:



H-(I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

X is NR^3, $C(R^3)_2$, or O;

Y is C=O or lower alkyl;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl or heteroaryl, each of which may be optionally substituted with one or more substituents selected from the group consisting of H, halogen, amino, hydroxy, cyano, nitro, carboxylate, alkyl, alkenyl, alkynyl, cycloalkyl, cyclohexyl, alkoxy, mono and di-alkyl amino, phenyl, carboxamide, haloalkyl, haloalkoxy, and alkanoyl;

each R^2 is independently selected from CO_2R^3, $COAr^3$, $CONR^3R^4$, $(CH_2)_mAr^3$, $CH_2NR^3R^4$ or CH_2OR^4

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2R^7$ or $(CH_2)_pAr^3$;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

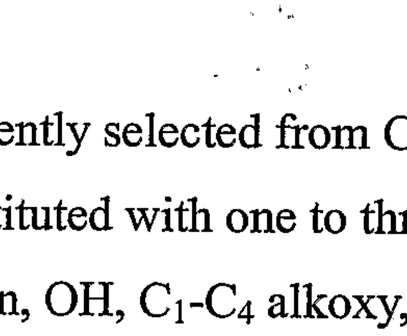
each R^6 is independently selected from hydrogen, $(CH_2)_qAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_qAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy; and

each q is independently 0 or 1.

12. A compound of formula J- (I) or pharmaceutical salt thereof



J- (I)

wherein,

Ar^1 is cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

R^1 is Ar^2 or lower alkyl optionally substituted with Ar^2;

each Ar^2 is independently selected from cycloalkyl, aryl, heterocyclyl, or heteroaryl each optionally substituted with one or more substituents;

each R^2 is independently selected from $(CH_2)_mCO_2R^3$, $(CH_2)_mCOAr^3$, $(CH_2)_mCONR^3R^4$, $(CH_2)_mAr^3$ or $(CH_2)_nNR^3R^4$;

each R^3 is independently selected from H, or lower alkyl;

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2)R^7$ or $(CH_2)_pAr^3$; or

each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atoms in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or more lower alkyl groups;

each Ar^3 is independently cycloalkyl, aryl, heterocyclyl, or heteroaryl, each optionally substituted with one or more substituents;

each m is independently 0 or 1;

each n is independently 1 or 2;

each p is independently 0 or 1;

each substituent for Ar^3 is independently selected from halogen, CN, NO_2, OR^5, SR^5, $S(O)_2OR^5$, NR^5R^6, cycloalkyl, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^5$, $C(O)NR^5R^6$, $OC(O)NR^5R^6$, $NR^5C(O)NR^5R^6$, $C(NR^5)NR^5R^6$, $NR^5C(NR^6)NR^5R^6$, $S(O)_2NR^5R^6$, R^7, $C(O)R^7$, $NR^6C(O)R^7$, $S(O)R^7$, or $S(O)_2R^7$;

each R^5 is independently selected from hydrogen or lower alkyl optionally substituted with one or more substituent independently selected from halogen,

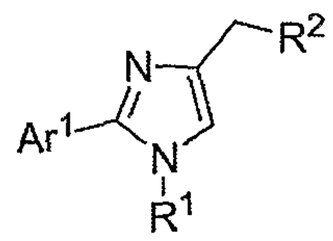
OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, $(CH_2)_pAr^4$, or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl;

each R^7 is independently selected from $(CH_2)_pAr^4$ or lower alkyl optionally substituted with one or more substituent independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or C_3-C_6 cycloalkyl; and

each Ar^4 is independently selected from C_3-C_6 cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three substituents independently selected from halogen, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino or 1,2-methylenedioxy.

13. The compound of formula J- (I) in claim 12



J- (I)

wherein,

Ar^1 is aryl or heteroaryl each optionally substituted with one to three substituents;

R^1 is Ar^2;

each Ar^2 is independently selected from aryl or heteroaryl each optionally substituted with one to three substituents;

R^2 is $(CH_2)_nNR^3R^4$ and n is 1 wherein,

each R^4 is independently selected from H, lower alkyl, $C(O)OR^5$, $C(O)NR^5R^6$, $S(O)_2NR^5R^6$, $C(O)R^7$, $S(O)_2)R^7$ or $(CH_2)_pAr^3$; or

each R^3 and R^4 are taken together with the nitrogen atom to which they are both attached to form a 4-7 membered heterocyclic ring wherein,

one carbon atoms in each heterocyclic ring is optionally a NR^4, O or S and each heterocyclic ring is optionally substituted with one or two lower alkyl groups;

each p is independently 0 or 1; and

each Ar^3 is independently selected from aryl or heteroaryl, each optionally substituted with one to three substituents.

14. The compound of any of claims 1-13 that is any of those in Tables A-J herein.

15. A method of inhibiting calcium channel activity comprising contacting a compound of any of claims 1 to 14 with a calcium channel.

16. A method of inhibiting calcium channel activity in a subject comprising administering to the subject an effective amount of a compound of any of claims 1 to 14.

17. A method of treating a calcium channel mediated disease in a subject comprising administering to the subject an effective amount of a compound of any of claims 1 to 14.

18. The method of any of claims 15-17 wherein the calcium channel is Ca_v1.

19. The method of any of claims 15-17 wherein the calcium channel is $Ca_v1.2$ or $Ca_v1.3$.

20. The method of claim 17 wherein the Ca_v1 calcium channel mediated disease or disease symptom is a cognitive function or nervous system disease or disease symptom.

21. The method of claim 17 wherein the $Ca_v1.2$ or $Ca_v1.3$ calcium channel mediated disease or disease symptom is a cognitive function or nervous system disease or disease symptom.

22. The method of claim 17 wherein the Ca_v1 calcium channel mediated disease or disease symptom is a cardiovascular disease or disease symptom.

23. The method of claim 17 wherein the $Ca_v1.2$ or $Ca_v1.3$ calcium channel mediated disease or disease symptom is a cardiovascular disease or disease symptom.

24. A method of treating Ca_v1 calcium channel mediated angina, congestive heart failure, or myocardial ischemia in a subject comprising administering to the subject an effective amount of a compound of any claims 1 to 14.

25. A method of claim 24, wherein the Ca_v1 calcium channel is $Ca_v1.2$ or $Ca_v1.3$.

26. A method of treating Ca_v1 calcium channel mediated urinary incontinence or overactive bladder in a subject comprising administering to a subject an effective amount of a compound of any of claims 1 to 14.

27. A method of claim 26, wherein the Ca_v1 calcium channel is $Ca_v1.2$ or $Ca_v1.3$.

30. A method of treating Ca_v1 calcium channel atrial fibrillation in a subject comprising administering to a subject an effective amount of a compound of any claims 1 to 14.

31. A method of claim 30, wherein the Ca_v1 calcium channel is $Ca_v1.2$ or $Ca_v1.3$.

32. A method of treating Ca_v1 calcium channel mediated hypertension in a subject comprising administering to the subject an effective amount of a compound of any of claims 1 to 14.

33. A method of claim 32, wherein the Ca_v1 calcium channel is $Ca_v1.2$ or $Ca_v1.3$.

34. A method of making a compound of any of claims 1-14, comprising reacting an intermediate compound delineated herein with a reagent to provide a compound of any of claims 1-14 as defined herein.

35. A composition comprising a compound of any of claims 1-14 and a pharmaceutically acceptable carrier.

36. The composition of claim 35, further comprising an additional therapeutic agent.

37. A method of treating a disease or disease symptom in a subject comprising administering to the subject in need of such treatment an effective amount of a compound of any of claims 1-14.

38. The method of claim 37, wherein the disease or disease symptom is angina, hypertension, congestive heart failure, myocardial ischemia, atrial fibrillation, diabetes mellitus, urinary incontinence, overactive bladder, pulmonary disease, cognitive function, or a nervous system disorder.